**ANNEX I**

**LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTES OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES**

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Risperdal Consta | 12,5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 12,5 mg / 2ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Risperdal Consta | 25 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Risperdal Consta | 37,5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 37,5 mg / 2 ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Risperdal Consta | 50 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Rispolin Consta | 12,5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 12,5 mg / 2ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Rispolin Consta | 25 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Rispolin Consta | 37,5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 37,5 mg / 2 ml |
| Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75, 1232 Wien, Austria | Rispolin Consta | 50 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Belivon Consta | 25 mg | Powder and solvent for solution for injection | Intramuscular use | 25 mg / 2 ml |
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Belivon Consta | 37.5 mg | Powder and solvent for solution for injection | Intramuscular use | 37.5 mg / 2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Belivon Consta | 50 mg | Powder and solvent for solution for injection | Intramuscular use | 50 mg / 2 ml |
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Risperdal Consta | 25 mg | Powder and solvent for solution for injection | Intramuscular use | 25 mg / 2 ml |
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Risperdal Consta | 37.5 mg | Powder and solvent for solution for injection | Intramuscular use | 37.5 mg / 2 ml |
| Belgium | Janssen Cilag N.V. Roderveldlaan 1, 2600 Berchem, Belgium | Risperdal Consta | 50 mg | Powder and solvent for solution for injection | Intramuscular use | 50 mg / 2 ml |
| Bulgaria | Johnson & Johnson D.O.O. Smartinska cesta 53, 1000 Ljubljana, Slovenia | Rispolept Consta | 25 mg | Powder and solvent for solution for injection | Intramuscular use | 25 mg / 2 ml |
| Bulgaria | Johnson & Johnson D.O.O. Smartinska cesta 53, 1000 Ljubljana, Slovenia | Rispolept Consta | 37.5 mg | Powder and solvent for solution for injection | Intramuscular use | 37.5mg / 2 ml |
| Bulgaria | Johnson & Johnson D.O.O. Smartinska cesta 53, 1000 Ljubljana, Slovenia | Rispolept Consta | 50 mg | Powder and solvent for solution for injection | Intramuscular use | 50 mg / 2 ml |
| Cyprus | Janssen-Cilag International NV, Belgium Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 25 mg | Powder for suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Cyprus | Janssen-Cilag International NV, Belgium Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 37.5 mg | Powder for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Cyprus | Janssen-Cilag International NV, Belgium Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 50 mg | Powder for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Czech | Janssen-Cilag s.r.o. | Risperdal Consta | 25 mg | Powder and solvent for | Intramuscular use | 25 mg / 2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Republic | Karla Engliše 3201/6,<br>15000 Praha 5, Czech Republic | 25 mg | | suspension for injection | | |
| Czech Republic | Janssen-Cilag s.r.o.<br>Karla Engliše 3201/6,<br>15000 Praha 5, Czech Republic | Risperdal Consta 37,5 mg | 37,5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Czech Republic | Janssen-Cilag s.r.o.<br>Karla Engliše 3201/6,<br>15000 Praha 5, Czech Republic | Risperdal Consta 50 mg | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Estonia | Johnson & Johnson UAB<br>Sheimynishkiu 1A<br>09312 Vilnius<br>Lithuania | Rispolept Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscular use | 25mg/2ml |
| Estonia | Johnson & Johnson UAB<br>Sheimynishkiu 1A<br>09312 Vilnius<br>Lithuania | Rispolept Consta | 37,5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37,5mg/2ml |
| Estonia | Johnson & Johnson UAB<br>Sheimynishkiu 1A<br>09312 Vilnius<br>Lithuania | Rispolept Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50mg/2ml |
| Finland | Jansen-Cilag Oy<br>Metsänneidonkuja 8<br>02130 Espoo Finland | Risperdal Consta | 12.5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 12.5 mg / 2 ml |
| Finland | Jansen-Cilag Oy<br>Metsänneidonkuja 8<br>02130 Espoo Finland | Risperdal Consta | 25 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Finland | Jansen-Cilag Oy<br>Metsänneidonkuja 8<br>02130 Espoo Finland | Risperdal Consta | 37.5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 37,5 mg / 2 ml |
| Finland | Jansen-Cilag Oy<br>Metsänneidonkuja 8 | Risperdal Consta | 50 mg | Powder and solvent for prolonged-release | Intramuscular use | 50 mg / 2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| | 02130 Espoo Finland | | | suspension for injection | | |
| France | Janssen Cilag<br>1 rue Desmoulins<br>TSA 91003<br>92787 Issy les Moulineaux<br>Cedex 9<br>France | Risperdalconsta LP | 25 mg | Powder for suspension for injection | Intramuscular use | 25 mg/2 ml |
| France | Janssen Cilag<br>1 rue Desmoulins<br>TSA 91003<br>92787 Issy les Moulineaux<br>Cedex 9<br>France | Risperdalconsta LP | 37.5 mg | Powder for suspension for injection | Intramuscular use | 37.5 mg/2 ml |
| France | Janssen Cilag<br>1 rue Desmoulins<br>TSA 91003<br>92787 Issy les Moulineaux<br>Cedex 9<br>France | Risperdalconsta LP | 50 mg | Powder for suspension for injection | Intramuscular use | 50 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperdal Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperdal Consta | 37.5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperdal Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg/2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperidon-Janssen Consta | 25. mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperidon-Janssen Consta | 37.5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Risperidon-Janssen Consta | 50. mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Rispon-Janssen Consta | 25. mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Rispon-Janssen Consta | 37.5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg/2 ml |
| Germany | Janssen-Cilag GmbH<br>Raiffeisenstr. 8<br>41470 Neuss<br>Germany | Rispon-Janssen Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg/2 ml |
| Greece | Janssen-Cilag Pharmaceuticals Aebe Eirinis Avenue 56, Pefki, 15121, Greece | Risperdal Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg/2 ml |
| Greece | Janssen-Cilag Pharmaceuticals Aebe Eirinis Avenue 56, Pefki, 15121, Greece | Risperdal Consta | 37.5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg/2 ml |
| Greece | Janssen-Cilag Pharmaceuticals | Risperdal Consta | 50 mg | Powder and solvent for | Intramuscular use | 50 mg/2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| | Aebe Eirinis Avenue 56, Pefki, 15121, Greece | | | suspension for injection | | |
| Iceland | Janssen-Cilag AB<br>c/oVistor hf.Hörgatúni 2<br>Garðabær, Iceland | Risperdal Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Iceland | Janssen-Cilag AB<br>c/oVistor hf.Hörgatúni 2<br>Garðabær, Iceland | Risperdal Consta | 37,5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Iceland | Janssen-Cilag AB<br>c/oVistor hf.Hörgatúni 2<br>Garðabær, Iceland | Risperdal Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Ireland | Janssen-Cilag Ltd<br>Saunderton<br>High Wycombe<br>Buckinghamshire HP14 4HJ<br>United Kingdom | Risperdal Consta | 25 mg | Powder for Suspension for<br>Injection | Intramuscular use | 25 mg / 2 ml |
| Ireland | Janssen-Cilag Ltd<br>Saunderton<br>High Wycombe<br>Buckinghamshire HP14 4HJ<br>United Kingdom | Risperdal Consta | 37.5 mg | Powder for Suspension for Injection | Intramuscular use | 37.5 mg / 2 ml |
| Ireland | Janssen-Cilag Ltd<br>Saunderton<br>High Wycombe<br>Buckinghamshire HP14 4HJ<br>United Kingdom | Risperdal Consta | 50 mg | Powder for Suspension for<br>Injection | Intramuscular use | 50 mg / 2 ml |
| Italy | Janssen Cilag Spa<br>Via Michelangelo Buonarroti n. 23<br>Cologno Monzese, 20093, Milano, Italy | Risperdal | 25 mg | Powder for Suspension for<br>Injection | Intramuscular use | 25 mg/2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Italy | Janssen Cilag Spa<br>Via Michelangelo Buonarroti n. 23<br>Cologno Monzese, 20093, Milano, Italy | Risperdal | 37,5 mg | Powder for Suspension for<br>Injection | Intramuscular use | 37,5 mg/2 ml |
| Italy | Janssen Cilag Spa<br>Via Michelangelo Buonarroti n. 23<br>Cologno Monzese, 20093, Milano, Italy | Risperdal | 50 mg | Powder for Suspension for<br>Injection | Intramuscular use | 50 mg/2 ml |
| Latvia | UAB Johnson&Johnson, Šeimyniškiu g.1A, Vilnius, Lithuania | Rispolept Consta | 25 mg | Prolonged release powder and solvent for suspension for injection | Intramuscular use | 25 mg/2ml |
| Latvia | UAB Johnson&Johnson, Šeimyniškiu g.1A, Vilnius, Lithuania | Rispolept Consta | 50 mg | Prolonged release powder and solvent for suspension for injection | Intramuscular use | 50 mg/2ml |
| Latvia | UAB Johnson&Johnson, Šeimyniškiu g.1A, Vilnius, Lithuania | Rispolept Consta | 37,5 mg | Prolonged release powder and solvent for suspension for injection | Intramuscular use | 37,5 mg/2ml |
| Lithuania | UAB „Johnson & Johnson“, Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania | Rispolept Consta | 25 mg | Prolonged-release powder and solvent for solution for injection | Intramuscular use | 25 mg / 2 ml |
| Lithuania | UAB „Johnson & Johnson“, Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania | Rispolept Consta | 37,5 mg | Prolonged-release powder and solvent for solution for injection | Intramuscular use | 37.5 mg / 2 ml |
| Lithuania | UAB „Johnson & Johnson“, Šeimyniškių g. 1A, LT-09312 Vilnius, Lithuania | Rispolept Consta | 50 mg | Prolonged-release powder and solvent for solution for injection | Intramuscular use | 50 mg / 2 ml |
| Malta | Janssen Cilag International NV Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 25 mg | Powder for suspension for injection | Intramuscular use | 25mg/2ml |

| **Member State** | **Marketing Authorisation Holder** | **Invented Name** | **Strength** | **Pharmaceutical Form** | **Route of administration** | **Content (concentration)** |
|---|---|---|---|---|---|---|
| Malta | Janssen Cilag International NV Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 37.5 mg | Powder for suspension for injection | Intramuscular use | 37.5mg/2ml |
| Malta | Janssen Cilag International NV Turnhoutseweg 30, 2340 Beerse, Belgium | Risperdal Consta | 50 mg | Powder for suspension for injection | Intramuscular use | 50mg/2ml |
| Netherlands | Janssen-Cilag<br>Dr. Paul Janssenweg 150<br>PO Box 90240<br>5000 LT Tilburg<br>The Netherlands | Risperdal Consta | 12.5 mg | Powder and solution for suspension and injection | Intramuscular use | 12.5 mg / 2 ml |
| Netherlands | Janssen-Cilag<br>Dr. Paul Janssenweg 150<br>PO Box 90240<br>5000 LT Tilburg<br>The Netherlands | Risperdal Consta | 25 mg | Powder and solution for suspension and injection | Intramuscular use | 25 mg / 2 ml |
| Netherlands | Janssen-Cilag<br>Dr. Paul Janssenweg 150<br>PO Box 90240<br>5000 LT Tilburg<br>The Netherlands | Risperdal Consta | 37.5 mg | Powder and solution for suspension and injection | Intramuscular use | 37.5 mg / 2 ml |
| Netherlands | Janssen-Cilag<br>Dr. Paul Janssenweg 150<br>PO Box 90240<br>5000 LT Tilburg<br>The Netherlands | Risperdal Consta | 50 mg | Powder and solution for suspension and injection | Intramuscular use | 50 mg / 2 ml |
| Norway | Janssen-Cilag AS<br>Hoffsveien 1D<br>0275 Oslo Norway | Risperdal Consta | 25 mg | Prolonged-release powder (microspheres) and a solvent for suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Norway | Janssen-Cilag AS | Risperdal Consta | 37,5 mg | Prolonged-release | Intramuscular use | 37.5 mg / 2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| | Hoffsveien 1D<br>0275 Oslo Norway | | | powder (microspheres) and a solvent for suspension for injection | | |
| Norway | Janssen-Cilag AS<br>Hoffsveien 1D<br>0275 Oslo Norway | Risperdal Consta | 50 mg | Prolonged-release powder (microspheres) and a solvent for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Poland | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30<br>2340 Beerse<br>Belgium | Rispolept Consta | 25 mg | Prolonged-release microcapsule and solvent for suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Poland | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30<br>2340 Beerse<br>Belgium | Rispolept Consta | 37,5 mg | Prolonged-release microcapsule and solvent for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Poland | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30<br>2340 Beerse<br>Belgium | Rispolept Consta | 50 mg | Prolonged-release microcapsule and solvent for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Portugal | Janssen Farmacêutica Portugal Lda.<br>Estrada Consiglieri Pedroso<br>69 A - Queluz de Baixo<br>2734-503 Barcarena<br>Portugal | Risperdal Consta | 25 mg | Pó e veículo para suspensão injectável | Intramuscular use | 25 mg / 2 ml |
| Portugal | Janssen Farmacêutica Portugal Lda.<br>Estrada Consiglieri Pedroso<br>69 A - Queluz de Baixo<br>2734-503 Barcarena<br>Portugal | Risperdal Consta | 37.5 mg | Pó e veículo para suspensão injectável | Intramuscular use | 37.5 mg / 2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| Portugal | Janssen Farmacêutica Portugal Lda.<br>Estrada Consiglieri Pedroso<br>69 A - Queluz de Baixo<br>2734-503 Barcarena<br>Portugal | Risperdal Consta | 50 mg | Pó e veículo para suspensão injectável | Intramuscular use | 50 mg / 2 ml |
| Romania | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30, 2340 Beerse,<br>Belgium | Rispolept Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Romania | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30, 2340 Beerse,<br>Belgium | Rispolept Consta | 37.5 mg | Powder and solvent for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Romania | Janssen Pharmaceutica N.V.<br>Turnhoutseweg 30, 2340 Beerse,<br>Belgium | Rispolept Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscular use | 50 mg / 2 ml |
| Slovak Republic | Johnson & Johnson s.r.o.<br>Plynárenská 7/B<br>Bratislava<br>Slovak Republic | Risperdal Consta | 25 mg | Powder and solvent for suspension for injection | Intramuscural use | 25 mg / 2 ml |
| Slovak Republic | Johnson & Johnson s.r.o.<br>Plynárenská 7/B<br>Bratislava<br>Slovak Republic | Risperdal Consta | 37,5 mg | Powder and solvent for suspension for injection | Intramuscural use | 37.5 mg / 2 ml |
| Slovak Republic | Johnson & Johnson s.r.o.<br>Plynárenská 7/B<br>Bratislava<br>Slovak Republic | Risperdal Consta | 50 mg | Powder and solvent for suspension for injection | Intramuscural use | 50 mg / 2 ml |
| Slovenia | Johnson & Johnson d.o.o.,<br>Šmartinska 53, Ljubljana,<br>Slovenia | Risperdal Consta | 25 mg | Prolonged release powder and solvent for suspension for injection | Intramuscural use | 25 mg/2 ml |
| Slovenia | Johnson & Johnson d.o.o., | Risperdal Consta | 37,5 mg | Prolonged release | Intramuscural use | 37,5 mg/2 ml |

| Member State | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical Form | Route of administration | Content (concentration) |
|---|---|---|---|---|---|---|
| | Šmartinska 53, Ljubljana, Slovenia | | | powder and solvent for suspension for injection | | |
| Slovenia | Johnson & Johnson d.o.o., Šmartinska 53, Ljubljana, Slovenia | Risperdal Consta | 50 mg | Prolonged release powder and solvent for suspension for injection | Intramuscural use | 50 mg/2 ml |
| Spain | JANSSEN CILAG, SA<br>Paseo de las 12 estrellas, 5-7<br>Madrid, Spain | Risperdal Consta | 25 mg | Powder and solvent for solution for injection | Intramuscular use | 25 mg / 2 ml |
| Spain | JANSSEN CILAG, SA<br>Paseo de las 12 estrellas, 5-7<br>Madrid, Spain | Risperdal Consta | 37.5 mg | Powder and solvent for solution for injection | Intramuscular use | 37.5 mg / 2 ml |
| Spain | JANSSEN CILAG, SA<br>Paseo de las 12 estrellas, 5-7<br>Madrid, Spain | Risperdal Consta | 50 mg | Powder and solvent for solution for injection | Intramuscular use | 50 mg / 2 ml |
| Sweden | Janssen-Cilag AB<br>Box 7073<br>192 07 Sollentuna<br>Sweden | Risperdal Consta | 25 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 25 mg / 2 ml |
| Sweden | Janssen-Cilag AB<br>Box 7073<br>192 07 Sollentuna<br>Sweden | Risperdal Consta | 37,5 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| Sweden | Janssen-Cilag AB<br>Box 7073<br>192 07 Sollentuna<br>Sweden | Risperdal Consta | 50 mg | Powder and solvent for prolonged-release suspension for injection | Intramuscular use | 50 mg / 2 ml |
| United Kingdom | Janssen-Cilag Ltd.<br>Saunderton<br>High-Wycombe<br>Buckinghamshire HP 14 4HJ<br>United Kingdom | Risperdal Consta | 25 mg | Powder for suspension for injection | Intramuscular use | 25 mg / 2 ml |

| **Member State** | **Marketing Authorisation Holder** | **Invented Name** | **Strength** | **Pharmaceutical Form** | **Route of administration** | **Content (concentration)** |
|---|---|---|---|---|---|---|
| United Kingdom | Janssen-Cilag Ltd.<br>Saunderton<br>High-Wycombe<br>Buckinghamshire HP 14 4HJ<br>United Kingdom | Risperdal Consta | 37.5 mg | Powder for suspension for injection | Intramuscular use | 37.5 mg / 2 ml |
| United Kingdom | Janssen-Cilag Ltd.<br>Saunderton<br>High-Wycombe<br>Buckinghamshire HP 14 4HJ<br>United Kingdom | Risperdal Consta | 50 mg | Powder for suspension for injection | Intramuscular use | 50 mg / 2 ml |

# ANNEX II

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

## SCIENTIFIC CONCLUSIONS

## OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF RISPERDAL CONSTA AND ASSOCIATED NAMES (SEE ANNEX I)

Risperdal Consta (risperidone) is a benzisoxazole derivative with potent combined serotonin 5HT2A and dopamine D2 receptor-blocking properties. It is an effective atypical antipsychotic that is well tolerated, based on extensive clinical experience including long-term use. The authorised formulation of Risperdal Consta is a prolonged-release formulation for intramuscular (i.m.) injection containing 12.5, 25, 37.5, or 50 mg risperidone. The intramuscular long-acting injection (LAI) formulation provides slow and steady release of risperidone over a period of several weeks. The Referral procedure under Article 30 of Directive 2001/83/EC, as amended for Risperdal Consta was initiated in order to resolve divergences amongst the nationally authorised Product Information texts across the EU and EEA Member States, in particular with respect to indications, special warnings and precautions for use and interaction with other medicinal products and other forms of interaction. The CHMP assessed the proposed wording provided by the MAH, and particular attention was given to the following issues:

For section 4.1, the indication "schizophrenic disorders" was assessed in details, as the existing divergences were likely to have implications for the selection of the treatment population and for the dose regiment and concomitant treatments. The CHMP assessed the MAH responses and the submitted data, noting that Risperdal Consta was developed for the maintenance treatment of schizophrenia and adopting a harmonised wording that conveys the concept of a therapy to be administered after a disease has been brought under control. It was considered shown that it is not mandatory for patients to have been stabilised on oral medications, and even preferable that patients be switched to the long-acting injectable Risperdal Consta treatment, to increase adherence to the treatment. However, the CHMP requested the MAH to further discuss the proposed wording of the indication, and the need to establish tolerability with oral risperidone prior to initiating treatment with Risperdal Consta. The MAH provided further justifications, being of the position that restricting the use of Risperdal Consta to patients with an initial treatment response to oral risperidone would be unjustified and would introduce an unnecessary and potentially prolonged additional step for the prescribing physicians, delaying access of Risperdal Consta to those patients who may not be adherent to their oral medication and who may be among the most suitable candidates for a long-acting injectable medication. Based on the submitted data, the CHMP was of the opinion that the presented clinical data show that patients stabilised with any antipsychotic medication (oral or depot formulations) can safely be switched to Risperdal Consta and achieve a clinical benefit similar to that seen in patients being switched from oral risperidone and without a higher incidence of clinical deterioration. The CHMP agreed that no non-inferiority study is required and the following wording for section 4.1 was adopted:

*"Risperdal Consta is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics".*

The CHMP further assessed data from patients switched to Risperdal Consta without stabilisation on oral risperidone, and concluded that sufficient antipsychotic coverage should be ensured during a lag period following the first Risperdal Consta injection. The length of the oral supplementation period was also discussed and the CHMP concluded that 3 weeks is the most appropriate length, leading neither to an overdose at the end of the oral supplementation period in those patients who have a relatively early release, nor to clinically relevant 'underdosing' in patients for whom the main release starts from 4 weeks onwards only, given the relatively long half-life of the active moiety following oral risperidone.

The need for increased patient monitoring during the switch period was discussed and the CHMP considered that the data provided showed no worsening in clinical symptoms after the therapy with long-acting risperidone was initiated. According to various treatment guidelines of schizophrenia, the switch of antipsychotic treatment in patients with schizophrenia requires "per se" the increased

monitoring of therapy by qualified physicians and the CHMP was therefore of the opinion that due to nature of the illness and long-term experience with treatment of schizophrenia by atypical antipsychotics, proper monitoring of therapy after switching antipsychotic treatment can be expected, without being explicitly mentioned in the SPC.

For section 4.2, the CHMP discussed the Risperdal Consta starting dose (25 mg, intramuscular, every 2 weeks), considering the data provided by the MAH, and was of the opinion that the recommendation in the SPC that treatment should be started with the dose of 25 mg every two weeks should be maintained. Relatively constant dose-response after Risperdal Consta treatment using doses from 25 to 75 mg is considered to be established and the CHMP agreed that good medical practice would be to start patients at the lowest effective dose and to increase the dose only if the response is insufficient. This was supported by results from the switching studies and since this product has been on the market for several years already, its efficacy and safety have been already confirmed. The CHMP was also of the opinion that the proposed wording of the SPC gives enough flexibility to the treating physician to start with the dose of 25 mg or higher.

Regarding the precise correspondence of an oral risperidone dose to a specific dose of Risperdal Consta, a wording in the SPC was adopted, reflecting the available efficacy and safety data and the results of clinical studies, to guide the choice of starting dose of Risperdal Consta:

*"For most patients the recommended dose is 25 mg intramuscular every two weeks. For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg Risperdal Consta, while patients treated with higher oral doses should be considered for the higher Risperdal Consta dose of 37.5 mg.*

*Where patients are not currently taking oral risperidone, the oral pre-treatment dosage should be considered when choosing the i.m. starting dose. The recommended starting dose is 25 mg Risperdal Consta every two weeks. Patients on higher dosages of the used oral antipsychotic should be considered for the higher Risperdal Consta dose of 37.5 mg."*

The CHMP also assessed the proposed 12.5 mg dosing, in particular with regards to the elderly population, and considered that the 12.5 mg dose of Risperdal Consta would provide additional dosing flexibility but stressed that this dose is intended only as a lower initial dose to establish tolerability, to be used mainly for patients with a higher sensitivity to the effects of the drug, either because of reduced metabolism/excretion, or in patients with an intrinsic lower tolerability to psychotropic medication. This was reflected in the harmonised wording of the SPC, along with the statement *"The efficacy of the 12.5 mg dose has not been investigated in clinical trials"*. Furthermore, the PK of Risperdal Consta in the elderly population was adequately described, and it was shown that the pharmacokinetics in the population > 65 years are comparable to the population < 65 years. Due to the known efficacy and safety profile of risperidone, this additional dose is approvable without its own efficacy data and can be based solely on the PK data.

The CHMP assessed the need for a warning, advising against the use of Risperdal Consta in acute exacerbations of schizophrenia, but considered it to potentially raise a safety concern that is not valid or clinically justified and that there are no particular risks associated with using Risperdal Consta in acute exacerbations of schizophrenia that warrant a warning. If Risperdal Consta is used in accordance with the SPC recommendations for dosing, no particular safety or efficacy risks for the patient would be foreseen, even if acutely ill. The CHMP adopted the following text in section 4.2:

*"Risperdal Consta should not be used in acute exacerbations of schizophrenia without ensuring sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic during the three-week lag period following the first Risperdal Consta injection."*

Finally, the CHMP discussed the use of Risperdal Consta in patients previously treated with oral risperidone at doses ≥6mg/day and noted that the provided efficacy data of these patients, when

switched to Risperdal Consta, were not different from the data obtained after previous oral risperidone treatment, despite the high probability of lower plasma level of risperidone being reached. In addition, long-acting risperidone offers an advantage in increased compliance to the treatment, which could result in more stable plasma levels of risperidone. The CHMP was also of the opinion that doses of risperidone > 8 mg/day should not be routinely used and should be restricted to certain group of patients. In conclusion, the CHMP was not in favour of restricting the use of long-acting risperidone for patients who were administered with 6 mg risperidone per day.

The CHMP assessed the data provided on the use of Risperdal Consta in elderly patients and was of the opinion that no significant trend of increased adverse events according to the age of patients or dose of Risperdal Consta were identified. All differences were accordingly justified and the proposed wording in the SPC is acceptable. The MAH presented a table summarising the results of total PANSS score from RIS-INT-61, broken down by dose level for the dose groups 25 mg, 50 mg and 75 mg. Two additional tables provided data showing that treatment is non-inferior to risperidone oral treatment for the changes in positive and negative symptoms subscales of PANSS. The CHMP considered that the requested efficacy analysis had been provided and that the efficacy of Risperdal Consta was shown in all doses separately.

For section 4.3, the CHMP discussed the relevance of a Contraindication warning for patients with high risk factors for cerebrovasular adverse events. Because Risperdal Consta has not been studied in elderly patients with dementia, it is therefore not indicated for use in this group of patients, as stated in Section 4.4 of the proposed SPC and in line with the current CHMP SPC guideline. The CHMP agreed that the presence of cerebrovascular risk factors is poorly predictive for a risperidone-mediated increased cerebrovascular risk and was therefore of the opinion that a contraindication for Risperdal Consta in patients with high risk factors for cerebrovascular events was not justified.

For section 4.4, the CHMP implemented the wording on tardive dyskinesia, agreed upon by the Pharmacovigilance Working Party. The CHMP further assessed the need for special mention of hyperprolactinaemia and stimulation of cell growth in breast tumours linked to prolactin. The CHMP considered the MAH responses and agreed that although data may suggest that prolactin is involved in breast cancer etiology, further studies are required to establish a formal link, and therefore adopted the following wording, addressing the potential risks of hyperprolactinaemia, although without specific inclusion of prolactinoma and breast cancer:

*"Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with a relevant medical history. Risperdal should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possibly prolactin-dependent tumours."*

For section 4.6, the CHMP discussed the wording, moving the mention of galactorrhea to section 4.8 and adopting the following harmonised wording:

*"It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast-milk in small quantities. There are no data available on adverse effects in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child."*

For section 4.8, the CHMP assessed and harmonised the wording. The CHMP predominantly agreed to the proposed grouping of terms of adverse events, but nevertheless considered that "bundle branch block left" should not be separated from "bundle block right" as the different clinical management is not essential. "Sedation" should be separated from "somnolence" and not grouped by the term "sedation". Furthermore, **«** Anxiety » and « nervousness » should be separated and not grouped by the term "anxiety". Finally, « Extrapyramidal symptoms » should be the grouped term in the subparagraph Nervous System Disorders and the single symptoms should be mentioned with an

asterix. As already mentioned, hypersalivation/ drooling should be added to « EPS » as otherwise incidence of EPS is underestimated.

All sections of the SPC were thoroughly assessed and all revisions were implemented accordingly in the Labelling and in the Package Leaflet, achieving a harmonised Product Information text. Based on the available data, the CHMP is of the opinion that all raised question were adequately addressed and that the harmonised Product Information wording is acceptable.

**GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET**

Whereas

- the scope of the referral was the harmonisation of the Summaries of Products Characteristics, labelling and package leaflet,

- the Summaries of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Risperdal Consta and associated names (see Annex I).

**ANNEX III**

**SUMMARY OF PRODUCT CHARACTERISTICS,**
**LABELLING AND PACKAGE LEAFLET**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

RISPERDAL CONSTA and associated names (see Annex I) 12.5 mg powder and solvent for prolonged-release suspension for intramuscular injection
[See Annex I – To be completed nationally]

RISPERDAL CONSTA and associated names (see Annex I) 25 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 37.5 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 50 mg powder and solvent for prolonged-release suspension for intramuscular injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[To be completed nationally]

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

[To be completed nationally]

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

RISPERDAL CONSTA is indicated for the maintenance treatment of schizophrenia in patients currently stabilised with oral antipsychotics.

### 4.2 Posology and method of administration

*Adults*
Starting dose:
For most patients the recommended dose is 25 mg intramuscular every two weeks. For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg RISPERDAL CONSTA, while patients treated with higher oral doses should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

Where patients are not currently taking oral risperidone, the oral pre-treatment dosage should be considered when choosing the i.m. starting dose. The recommended starting dose is 25 mg RISPERDAL CONSTA every two weeks. Patients on higher dosages of the used oral antipsychotic should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

A lower initial dose of 12.5 mg may be appropriate when clinical factors warrant dose adjustment, such as in patients with hepatic or renal impairment, for certain drug interactions that increase risperidone plasma concentrations (see section 4.5), or in patients who have a history of poor tolerability to psychotropic medications. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2).

RISPERDAL CONSTA should not be used in acute exacerbations of schizophrenia without ensuring sufficient antipsychotic coverage with oral risperidone or the previous antipsychotic during the three-week lag period following the first RISPERDAL CONSTA injection.

Maintenance dose:
For most patients the recommended dose is 25 mg intramuscular every two weeks. Some patients may benefit from the higher doses of 37.5 mg or 50 mg. Upward dosage adjustment should not be made more frequently than every 4 weeks. The effect of this dose adjustment should not be anticipated earlier than 3 weeks after the first injection with the higher dose. No additional benefit was observed with 75 mg in clinical trials. Doses higher than 50 mg every 2 weeks are not recommended.

In patients with clinical factors such as hepatic or renal impairment or certain drug interactions that increase risperidone plasma concentrations (see section 4.5), dose reduction as low as 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

*Elderly*
No dose adjustment is required. The recommended dose is 25 mg intramuscularly every two weeks. Where patients are not currently taking oral risperidone, the recommended dose is 25 mg RISPERDAL CONSTA every two weeks. For those patients on a fixed dose of oral risperidone for two weeks or more, the following conversion scheme should be considered. Patients treated with a dosage of 4 mg or less oral risperidone should receive 25 mg RISPERDAL CONSTA, while patients treated with higher oral doses should be considered for the higher RISPERDAL CONSTA dose of 37.5 mg.

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2). RISPERDAL CONSTA clinical data in elderly are limited. RISPERDAL CONSTA should be used with caution in elderly.

*Hepatic and renal impairment*
RISPERDAL CONSTA has not been studied in hepatically and renally impaired patients.

If hepatically or renally impaired patients require treatment with RISPERDAL CONSTA, a starting dose of 0.5 mg twice daily oral risperidone is recommended during the first week. The second week 1 mg twice daily or 2 mg once daily can be given. If an oral total daily dose of at least 2 mg is well tolerated, an injection of 25 mg RISPERDAL CONSTA can be administered every 2 weeks.

Alternatively, a starting dose of RISPERDAL CONSTA of 12.5 mg may be appropriate. The efficacy of the 12.5 mg dose has not been investigated in clinical trials.

Sufficient antipsychotic coverage should be ensured during the three-week lag period following the first RISPERDAL CONSTA injection (see section 5.2).

*Paediatric population*
RISPERDAL CONSTA is not recommended for use in children below 18 years of age due to a lack of data on safety and efficacy.

Method of administration

RISPERDAL CONSTA should be administered every two weeks by deep intramuscular gluteal injection using the enclosed safety needle. Injections should alternate between the buttocks. Do not administer intravenously (see section 4.4 and section 6.6).

For instructions on preparation and handling RISPERDAL CONSTA, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

## 4.4 Special warnings and precautions for use

For risperidone-naive patients, it is recommended to establish tolerability with oral risperidone prior to initiating treatment with RISPERDAL CONSTA (see section 4.2).

Elderly patients with dementia
RISPERDAL CONSTA has not been studied in elderly patients with dementia, hence it is not indicated for use in this group of patients.

*Overall mortality*

Elderly patients with dementia treated with atypical antipsychotics have an increased mortality compared to placebo in a meta-analysis of 17 controlled trials of atypical antipsychotics, including oral RISPERDAL. In placebo-controlled trials with oral RISPERDAL in this population, the incidence of mortality was 4.0% for RISPERDAL-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).

*Concomitant use with furosemide*

In the oral RISPERDAL placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly patients with dementia.

Cerebrovascular adverse events (CVAE)

In placebo-controlled trials in elderly patients with dementia there was a significantly higher incidence (approximately 3-fold increased) of CVAEs, such as stroke (including fatalities) and transient ischaemic attack in patients treated with RISPERDAL compared with patients treated with placebo (mean age 85 years; range 73 to 97). The pooled data from six placebo-controlled studies in mainly elderly patients (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. RISPERDAL CONSTA should be used with caution in patients with risk factors for stroke.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during initiation of treatment. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g. heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease). The risk/benefit of further treatment with RISPERDAL CONSTA should be assessed if clinically relevant orthostatic hypotension persists.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including RISPERDAL CONSTA, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including RISPERDAL CONSTA, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycemia

Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during treatment with RISPERDAL CONSTA. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Hyperprolactinaemia

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. RISPERDAL CONSTA should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation
QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

RISPERDAL CONSTA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism
Priapism may occur with RISPERDAL CONSTA treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing RISPERDAL CONSTA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Weight gain

As with other antipsychotics, patients should be advised of the potential for weight gain. Weight should be measured regularly.

Renal or hepatic impairment

Although oral risperidone has been studied, RISPERDAL CONSTA has not been studied in patients with renal or liver insufficiency. RISPERDAL CONSTA should be administered with caution in this group of patients (see section 4.2).

Administration

Care must be taken to avoid inadvertent injection of RISPERDAL CONSTA into a blood vessel.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially 'sodium-free'.

## 4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies were performed with oral RISPERDAL.

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval, e.g., class Ia antiarrhythmics (e.g., quinidine, dysopiramide, procainamide), class III antiarrhythmics (e.g., amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressant (i.e., maprotiline), some antihistaminics, other antipsychotics, some antimalarials (i.e., chinice and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

*Potential for RISPERDAL CONSTA to affect other medicinal products*

Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

RISPERDAL CONSTA may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

RISPERDAL does not show a clinically relevant effect on the pharmacokinetics of lithium, valproate, digoxin or topiramate.

*Potential for other medicinal products to affect RISPERDAL CONSTA*

Carbamazepine has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. rifampicin, phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme as well as P-glycoprotein. When carbamazepine or other CYP 3A4 hepatic enzyme/P-glycoprotein (P-gp) inducers are initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Fluoxetine and paroxetine, CYP 2D6 inhibitors, increase the plasma concentration of risperidone, but less so of the active antipsychotic fraction. It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant fluoxetine or paroxetine is initiated or discontinued, the physician should re-evaluate the dosing of RISPERDAL CONSTA.

Verapamil, an inhibitor of CYP 3A4 and P-gp, increases the plasma concentration of risperidone.

Galantamine and donepezil do not show a clinically relevant effect on the pharmacokinetics of risperidone and on the active antipsychotic fraction.

Phenothiazines, tricyclic antidepressants, and some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction. Cimetidine and ranitidine increase the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction. Erythromycin, a CYP 3A4 inhibitor, does not change the pharmacokinetics of risperidone and the active antipsychotic fraction.

See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

## 4.6 Pregnancy and lactation

*Pregnancy*

There are no adequate data from the use of risperidone in pregnant women. According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently, newborns should be monitored carefully. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown. Therefore, RISPERDAL CONSTA should not be used during pregnancy unless clearly necessary.

*Lactation*

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse effects in breast-feeding infants. Therefore, the advantage of breast-feeding should be weighed against the potential risks for the child.

## 4.7 Effects on ability to drive and use machines

RISPERDAL CONSTA has minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

## 4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 1/10) are: Insomnia, anxiety, headache, upper respiratory tract infection, parkinsonism, depression, and akathisia.

The following are all the ADRs that were reported in clinical trials and postmarketing. The following terms and frequencies are applied: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available clinical trial data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions by System Organ Class and Frequency Category

| | |
|---|---|
| **Investigations** | |
| *Common* | Electrocardiogram abnormal, Blood prolactin increased[a], Blood glucose increased, Hepatic enzyme increased, Transaminases increased, Gamma-glutamyltransferase increased, Weight increased, Weight decreased |
| *Uncommon* | Electrocardiogram QT prolonged |
| **Cardiac disorders** | |
| *Common* | Atrioventricular block, Tachycardia |
| *Uncommon* | Bundle branch block, Atrial fibrillation, Bradycardia, Sinus bradycardia, Palpitations |
| **Blood and lymphatic system disorders** | |
| *Common* | Anaemia |
| *Uncommon* | Thrombocytopenia, Neutropenia |
| *Not known* | Agranulocytosis |
| **Nervous system disorders** | |
| *Very common* | Parkinsonism[b], Akathisia[b], Headache |
| *Common* | Dizziness, Sedation, Somnolence, Tremor, Dystonia[b], Tardive dyskinesia, Dyskinesia[b] |
| *Uncommon* | Convulsion, Syncope, Dizziness postural, Hypoaesthesia, Paraesthesia, Lethargy, Hypersomnia |
| **Eye disorders** | |
| *Common* | Vision blurred, Conjunctivitis |
| *Not known* | Retinal artery occlusion |
| **Ear and labyrinth disorders** | |
| *Common* | Vertigo |
| *Uncommon* | Ear pain |
| **Respiratory, thoracic and mediastinal disorders** | |
| *Common* | Dyspnoea, Cough, Nasal congestion, Pharyngolaryngeal pain |
| *Rare* | Sleep apnea syndrome |
| **Gastrointestinal disorders** | |
| *Common* | Vomiting, Diarrhoea, Constipation, Nausea, Abdominal pain, Dyspepsia, Toothache, Dry mouth, Stomach discomfort, Gastritis |
| *Rare* | Intestinal obstruction, Pancreatitis |
| **Renal and urinary disorders** | |
| *Common* | Urinary incontinence |
| **Skin and subcutaneous tissue disorders** | |
| *Common* | Rash, Eczema |
| *Uncommon* | Angioedema, Pruritus, Acne, Alopecia, Dry skin |
| **Musculoskeletal and connective tissue disorders** | |
| *Common* | Arthralgia, Back pain, Pain in extremity, Myalgia |
| *Uncommon* | Muscular weakness, Neck pain, Buttock pain, Musculoskeletal chest pain |
| **Endocrine disorders** | |
| *Rare* | Inappropriate antidiuretic hormone secretion |
| **Metabolism and nutrition disorders** | |
| *Uncommon* | Increased appetite, Decreased appetite |
| *Very rare* | Diabetic ketoacidosis |
| *Not known* | Water intoxication |
| **Infections and infestations** | |
| *Very common* | Upper respiratory tract infection |
| *Common* | Pneumonia, Influenza, Lower respiratory tract infection, Bronchitis, Urinary tract infection, Ear infection, Sinusitis, Viral infection |
| *Uncommon* | Cystitis, Gastroenteritis, Infection, Localised infection, Subcutaneous abscess |

| | |
|---|---|
| **Injury, poisoning and procedural complications** | |
| *Common* | Fall |
| *Uncommon* | Procedural pain |
| **Vascular disorders** | |
| *Common* | Hypertension, Hypotension |
| *Uncommon* | Orthostatic hypotension |
| **General disorders and administration site conditions** | |
| *Common* | Pyrexia, Peripheral oedema, Chest pain, Fatigue, Pain, Injection site pain, Asthenia, Influenza like illness |
| *Uncommon* | Feeling abnormal, Chest discomfort, Induration, Injection site induration, Sluggishness, Injection site reaction |
| *Rare* | Hypothermia |
| **Immune system disorders** | |
| *Uncommon* | Hypersensitivity |
| *Not known* | Anaphylactic reaction |
| **Hepatobiliary disorders** | |
| *Rare* | Jaundice |
| **Reproductive system and breast disorders** | |
| *Common* | Amenorrhoea, Erectile dysfunction, Galactorrhoea |
| *Uncommon* | Sexual dysfunction, Gynaecomastia |
| *Not known* | Priapism |
| **Psychiatric disorders** | |
| *Very common* | Depression, Insomnia, Anxiety |
| *Common* | Agitation, Sleep disorder |
| *Uncommon* | Mania, Libido decreased, Nervousness |

[a] Hyperprolactinemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, galactorrhea.

[b] Extrapyramidal disorder may occur: Parkinsonism (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal), akathisia (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia.
Dystonia includes dystonia, muscle spasms, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. Tremor includes tremor and parkinsonian rest tremor. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin.

The following is a list of additional ADRs associated with risperidone that have been identified as ADRs during clinical trials investigating the oral risperidone formulation (RISPERDAL) but were not determined to be ADRs in the clinical trials investigating RISPERDAL CONSTA.

Additional Adverse Drug Reactions Reported With Oral RISPERDAL but not With RISPERDAL CONSTA by System Organ Class

**Investigations**
Body temperature increased, Eosinophil count increased, White blood cell count decreased, Haemoglobin decreased, Blood creatine phosphokinase increased, Body temperature decreased

**Infections and Infestations**
Tonsillitis, Cellulitis, Otitis media, Eye infection, Acarodermatitis, Respiratory tract infection, Onychomycosis, Otitis media chronic

**Blood and Lymphatic Disorders**
Granulocytopenia

**Immune System Disorders**
Drug hypersensitivity
**Metabolism and Nutrition Disorders**
Anorexia, Polydipsia
**Psychiatric Disorders**
Confusional state, Listless, Anorgasmia, Blunted affect
**Nervous System Disorders**
Unresponsive to stimuli, Loss of consciousness, Neuroleptic malignant syndrome, Diabetic coma, Cerebrovascular accident, Depressed level of consciousness, Cerebral ischemia, Cerebrovascular disorder, Transient ischemic attack, Dysarthria, Disturbance in attention, Balance disorder, Speech disorder, Coordination abnormal, Movement disorder
**Eye Disorders**
Ocular hyperemia, Eye discharge, Eye swelling, Dry eye, Lacrimation increased, Photophobia, Visual acuity reduced, Eye rolling, Glaucoma
**Ear and Labyrinth Disorders**
Tinnitus
**Vascular Disorders**
Flushing
**Respiratory, Thoracic, and Mediastinal Disorders**
Wheezing, Pneumonia aspiration, Pulmonary congestion, Respiratory disorder, Rales, Epistaxis, Respiratory tract congestion, Hyperventilation, Dysphonia
**Gastrointestinal Disorders**
Dysphagia, Faecal incontinence, Faecaloma, Lip swelling, Cheilitis
**Skin and Subcutaneous Tissue Disorders**
Skin lesion, Skin disorder, Skin discoloration, Seborrheic dermatitis, Hyperkeratosis, Dandruff, Erythema
**Musculoskeletal, Connective Tissue, and Bone Disorders**
Rhabdomyolysis, Joint swelling, Posture abnormal, Joint stiffness
**Renal and Urinary Disorders**
Enuresis, Dysuria, Pollakiuria
**Reproductive System and Breast Disorders**
Ejaculation disorder, Vaginal discharge, Menstrual disorder
**General Disorders and Administration Site Conditions**
Generalised oedema, Face oedema, Gait disturbance, Thirst, Chills, Peripheral coldness, Drug withdrawal syndrome

*Class effects*

As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

*Weight gain*

In the 12-week double-blind, placebo-controlled trial, 9% of patients treated with RISPERDAL CONSTA, compared with 6% of patients treated with placebo, experienced a weight gain of ≥ 7% of body weight at endpoint. In the 1-year, open-label study of RISPERDAL CONSTA, changes in body weight in individual patients were generally within ±7% from baseline; 25% of patients had an increase in body weight of ≥ 7%.

## 4.9 Overdose

While overdose is less likely to occur with parenteral than with oral medicinal products, information pertaining to oral is presented.

*Symptoms*

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of oral RISPERDAL and paroxetine.

In case of acute overdose, the possibility of multiple drug involvement should be considered.

*Treatment*

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to RISPERDAL. Therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

*Pharmacotherapeutic group:* Other antipsychotics, ATC code: N05AX08

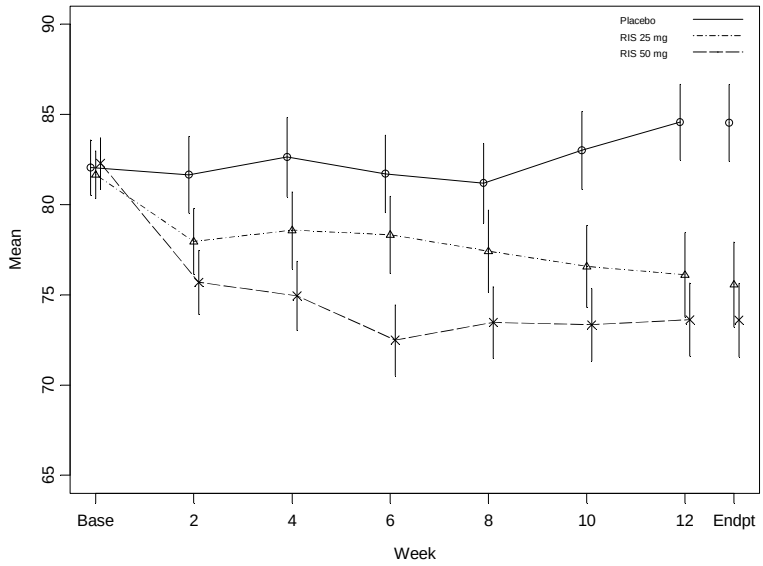
*Mechanism of action*

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2-adrenergic receptors. Risperidone has no affinity for cholinergic receptors. Although risperidone is a potent D2 antagonist, that is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

*Clinical efficacy*
The effectiveness of RISPERDAL CONSTA (25 mg and 50 mg) in the management of the manifestations of psychotic disorders (schizophrenia/schizoaffective disorder) was established in one 12-week, placebo-controlled trial in adult psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia.

In a 12-week comparative trial in stable patients with schizophrenia, RISPERDAL CONSTA was shown to be as effective as the oral tablet formulation. The long-term (50 weeks) safety and efficacy of RISPERDAL CONSTA was also evaluated in an open-label trial of stable psychotic inpatients and outpatients who met the DSM-IV criteria for schizophrenia or schizoaffective disorder. Over time efficacy was maintained with RISPERDAL CONSTA (Figure 1).

Figure 1. Mean in total PANSS score over time (LOCF) in patients with schizophrenia.




## 5.2 Pharmacokinetic properties

*Absorption*
The absorption of risperidone from RISPERDAL CONSTA is complete.

After a single intramuscular injection with RISPERDAL CONSTA, the release profile consists of a small initial release of risperidone (<1% of the dose), followed by a lag time of 3 weeks. The main release of risperidone starts from Week 3 onwards, is maintained from 4 to 6 weeks, and subsides by Week 7. Oral antipsychotic supplementation should therefore be given during the first 3 weeks of RISPERDAL CONSTA treatment (see section 4.2).

The combination of the release profile and the dosage regimen (intramuscular injection every two weeks) results in sustained therapeutic plasma concentrations. Therapeutic plasma concentrations remain until 4 to 6 weeks after the last RISPERDAL CONSTA injection.

After repeated intramuscular injections with 25 or 50 mg RISPERDAL CONSTA every two weeks, median trough and peak plasma concentrations of the active antipsychotic fraction fluctuated between 9.9-19.2 ng/ml and 17.9-45.5 ng/ml respectively. No accumulation of risperidone was observed during long term use (12 months) in patients who were injected with 25–50 mg every two weeks.

*Distribution*
Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha-1-acid glycoprotein. The plasma protein binding of risperidone is 90%; that of the active metabolite 9-hydroxy-risperidone is 77%.

*Biotransformation and elimination*
Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. *In vitro* studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after oral risperidone administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, risperidone plus 9-hydroxy-risperidone represent 35-45% of the orally administered dose. The remainder is inactive metabolites. The elimination phase is complete approximately 7 to 8 weeks after the last RISPERDAL CONSTA injection.

*Linearity*
The pharmacokinetics of risperidone following single doses of RISPERDAL CONSTA are linear in the dose range of 12.5-75 mg. The pharmacokinetics of risperidone are also linear in the dose range of 25-50 mg injected every 2 weeks.

*Elderly, hepatic and renal impairment*
A single-dose pharmacokinetic study with oral risperidone showed on average a 43% higher active antipsychotic fraction plasma concentrations, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly. Higher active antipsychotic fraction plasma concentrations and a reduced clearance of the active antipsychotic fraction by on average 60% were observed in patients with renal insufficiency. Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by about 35%.

*Pharmacokinetic/pharmacodynamic relationship*
There was no relationship between the plasma concentrations of the active antipsychotic fraction and the change in total PANSS (Positive And Negative Syndrome Scale) and total ESRS (Extrapyramidal Symptom Rating Scale) scores across the assessment visits in any of the phase-III trials where efficacy and safety was examined.

*Gender, race and smoking habits*
A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

## 5.3 Preclinical safety data

Similar to the (sub)chronic toxicity studies with oral risperidone in rats and dogs, the major effects of treatment with RISPERDAL CONSTA (up to 12 months of intramuscular administration) were prolactin-mediated mammary gland stimulation, male and female genital tract changes, and central nervous system (CNS) effects, related to the pharmacodynamic activity of risperidone.

Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

RISPERDAL CONSTA administration to male and female rats for 12 and 24 months produced osteodystrophy at a dose of 40 mg/kg/2 weeks. The effect dose for osteodystrophy in rats was on a $mg/m^2$ basis 8 times the maximum recommended human dose and is associated with a plasma exposure 2 times the maximum anticipated exposure in humans at the maximum recommended dose. No osteodystrophy was observed in dogs treated for 12 months with RISPERDAL CONSTA up to 20 mg/kg/2 weeks. This dose yielded plasma exposures up to 14 times the maximum recommended human dose.

There was no evidence of genotoxic potential.

As expected for a potent dopamine D2-antagonist, in oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen.

In an intramuscular carcinogenicity study with RISPERDAL CONSTA in Wistar (Hannover) rats (doses of 5 and 40 mg/kg/2 weeks), increased incidences of endocrine pancreas, pituitary gland, and adrenal medullary tumours were observed at 40 mg/kg, while mammary gland tumours were present at 5 and 40 mg/kg. These tumours observed upon oral and intramuscular dosing can be related to prolonged dopamine $D_2$ antagonism and hyperprolactinaemia. Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Hypercalcemia, postulated to contribute to an increased incidence of adrenal medullary tumours in RISPERDAL CONSTA-treated rats, was observed in both dose groups. There is no evidence to suggest that hypercalcemia might cause phaeochromocytomas in humans.

Renal tubular adenomas occurred in male rats treated with RISPERDAL CONSTA at 40 mg/kg/2 weeks. No renal tumours occurred in the low dose, the NaCl 0.9%, or the microspheres vehicle control group. The mechanism underlying the renal tumours in RISPERDAL CONSTA-treated male Wistar (Hannover) rats is unknown. A treatment-related increase in renal tumour incidence did not occur in the oral carcinogenicity studies with Wistar (Wiga) rats or in Swiss mice administered oral risperidone. Studies conducted to explore the substrain differences in the tumour organ profile suggest that the Wistar (Hannover) substrain employed in the carcinogenicity study differs substantially from the Wistar (Wiga) substrain employed in the oral carcinogenicity study with respect to spontaneous age-related non-neoplastic renal changes, serum prolactin increases, and renal changes in response to risperidone. There are no data suggesting kidney-related changes in dogs treated chronically with RISPERDAL CONSTA.

The relevance of the osteodystrophy, the prolactin-mediated tumours and of the presumed rat substrain-specific renal tumours in terms of human risk is unknown.

Local irritation at the injection site in dogs and rats was observed after administration of high doses of RISPERDAL CONSTA. In a 24-month intramuscular carcinogenicity study in rats, no increased incidence of injection site tumours was seen in either the vehicle or active groups.

In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

[To be completed nationally]

### 6.2 Incompatibilities

[To be completed nationally]

### 6.3 Shelf life

[To be completed nationally]

### 6.4 Special precautions for storage

[To be completed nationally]

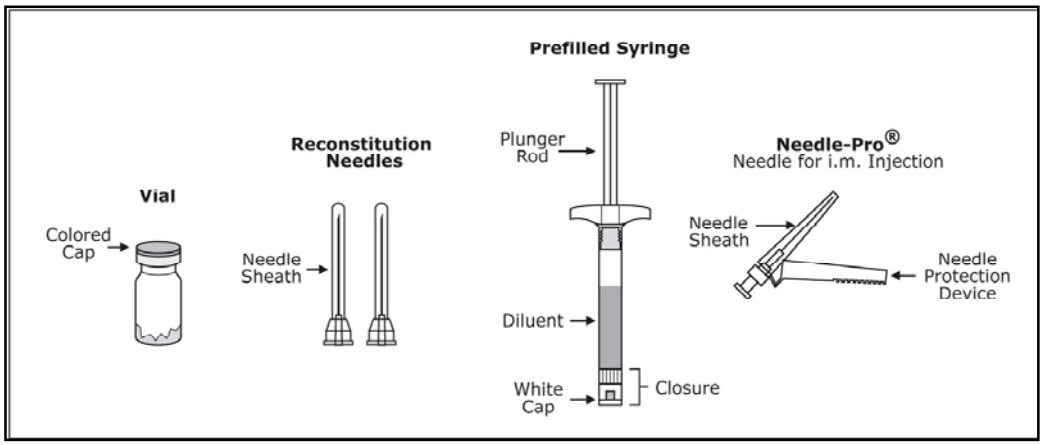
## 6.5 Nature and contents of container

[To be completed nationally]

## 6.6 Special precautions for disposal and other handling

**Instructions for Three Needle System**

RISPERDAL CONSTA extended release microspheres in the vial must be reconstituted **only** in the solvent in the syringe supplied in the dose pack, and must be administered **only** with the Needle-Pro safety needle supplied in the dose pack. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.

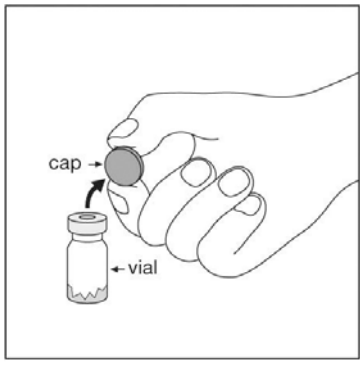



Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature prior to reconstitution.

Contents of the dose pack:

- One vial containing RISPERDAL CONSTA extended release microspheres
- Two Hypoint 20G 2” TW needles for reconstitution
- One prefilled syringe containing the solvent for RISPERDAL CONSTA
- One Needle-Pro needle for intramuscular injection (safety 20G 2” TW needle with needle protection device)

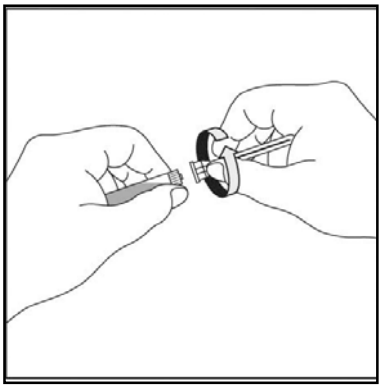
1. Flip off the plastic coloured cap from the vial.




2. Open the prefilled syringe by breaking the seal of the closure and remove the white cap together with the rubber tip cap inside.

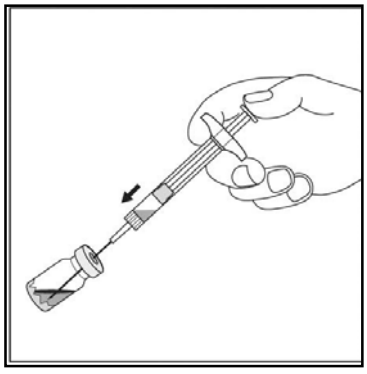

3. Open the cover of one reconstitution needle.

   *Keeping the syringe and needle aligned*, attach the needle with an easy clockwise twisting motion to the luer connection of the syringe.



4. Pull sheath away from the needle – do not twist.

   Inject the entire contents (solvent) of the syringe into the vial.

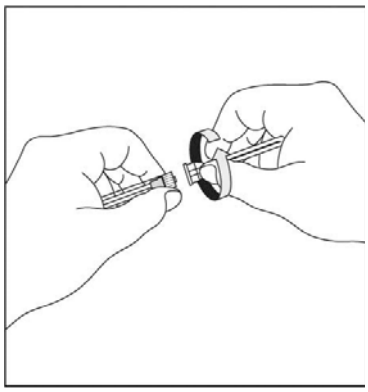


5. Withdraw the syringe with the reconstitution needle from the vial. Unscrew the needle from the syringe and discard the needle appropriately.

6. Open the cover of the second reconstitution needle.

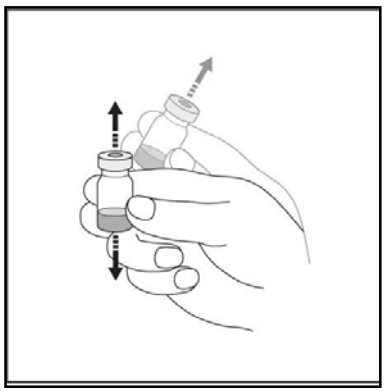
   *Keeping the empty syringe and needle aligned*, attach the second needle with an easy clockwise twisting motion to the luer connection of the syringe.

   Do not remove the sheath from the needle at this time.



7. Shake the vial vigorously for at least 10 seconds until obtaining a homogeneous suspension.

   Mixing is complete when the suspension appears uniform, thick, and milky in colour, and all the powder is fully dispersed.



**DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.**

8. Take the syringe and pull sheath away from the reconstitution needle – do not twist.
   Insert the reconstitution needle into the upright vial.
   Slowly withdraw the suspension from the vial in an upright, but slightly angled position as indicated in the picture to ensure that the entire contents are drawn up into the syringe.

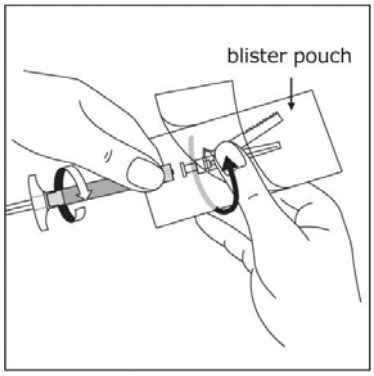
9. Withdraw the syringe with the reconstitution needle from the vial. Unscrew the needle from the syringe and discard the needle appropriately.

   For identification purposes, tear section of the vial label at the perforation and apply detached section to the syringe. Discard the vial appropriately.

10. Peel the blister pouch of the Needle-Pro device open half way. Grasp sheath using the plastic peel pouch.

    Attach the luer connection of the Needle-Pro device with an easy clockwise twisting motion to the syringe. Seat the needle firmly on the Needle-Pro device with a push and clockwise twist.

    *Prepare the patient for injection.*



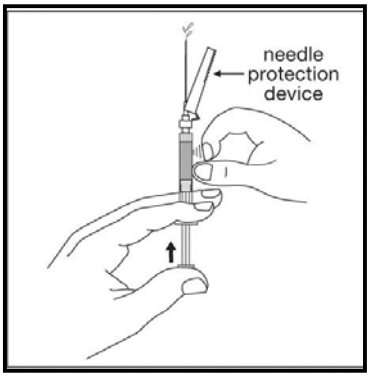

**RESUSPENSION OF RISPERDAL CONSTA WILL BE NECESSARY PRIOR TO ADMINISTRATION AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSPHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.**

11. Pull sheath away from the needle – do not twist sheath as needle may be loosened from Needle-Pro device.

    Tap the syringe gently to make any air bubbles rise to the top.

    Remove air bubbles from the syringe barrel by moving the plunger rod forward with the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the buttock of the patient.

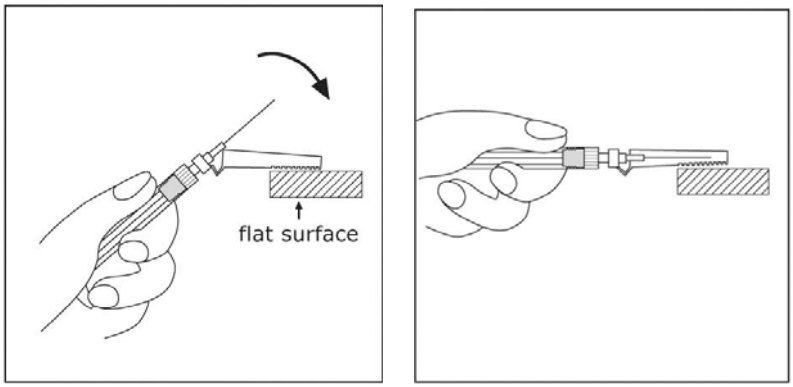
**DO NOT ADMINISTER INTRAVENOUSLY.**




**WARNING:** To avoid a needle stick injury with a contaminated needle, do not :

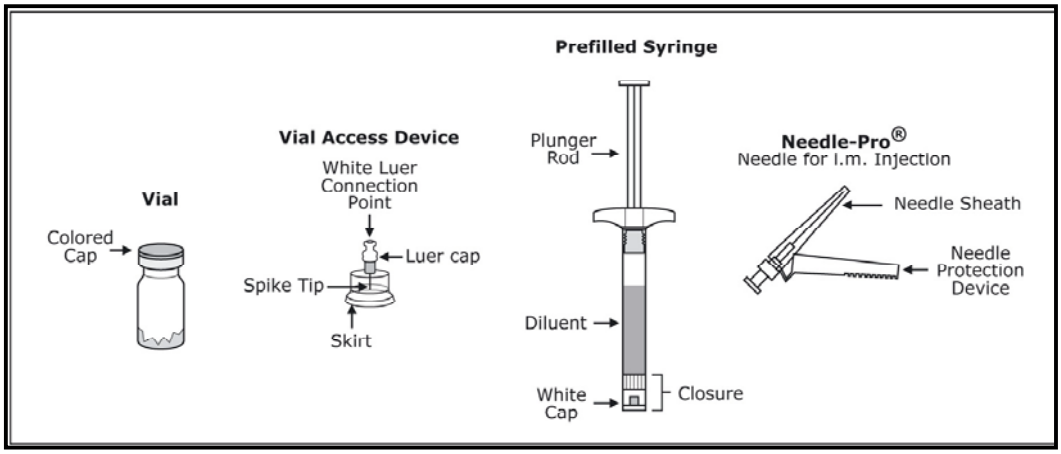
- Intentionally disengage the Needle-Pro device
- Attempt to straighten the needle or engage the Needle-Pro device if the needle is bent or damaged
- Mishandle the needle protection device that could lead to protrusion of the needle from it

12. After procedure is completed, press the needle into the needle protection device. Perform a one-handed technique by GENTLY pressing the needle protection device against a flat surface. As the needle protection device is pressed, the needle is firmly engaged into it. Visually confirm that the needle is fully engaged into the needle protection device. Immediately discard appropriately.




**Instructions for Needle-Free Vial Access Device**

RISPERDAL CONSTA extended release microspheres in the vial must be reconstituted **only** in the solvent in the syringe supplied in the dose pack, and must be administered **only** with the Needle-Pro safety needle supplied in the dose pack. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.

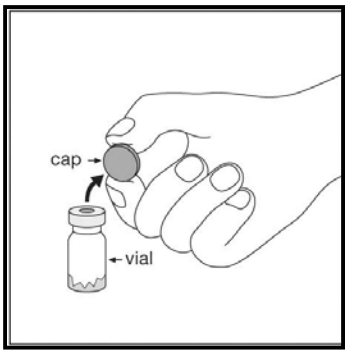



Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature prior to reconstitution.

Contents of the dose pack:

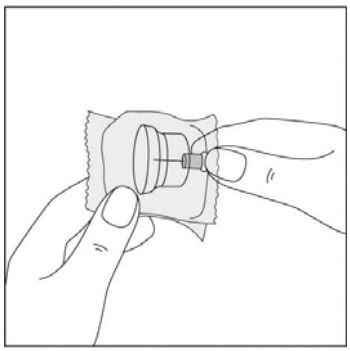
- One vial containing RISPERDAL CONSTA extended release microspheres
- One Alaris SmartSite needle-free vial access device for reconstitution
- One prefilled syringe containing the solvent for RISPERDAL CONSTA
- One Needle-Pro needle for intramuscular injection (safety 20G 2” TW needle-with needle protection device)

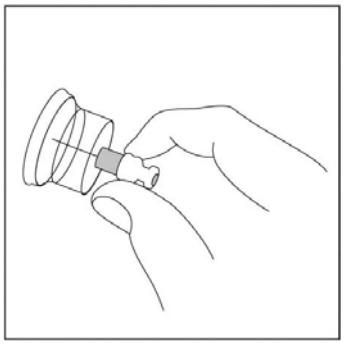
1. Flip off the plastic coloured cap from the vial.



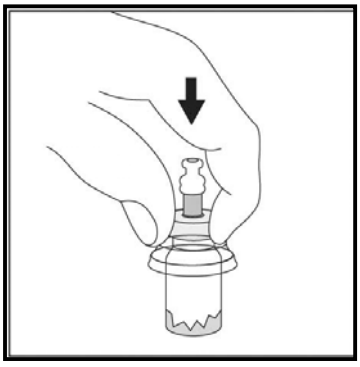

2. Peel back the blister pouch and remove the vial access device by holding the white luer cap.

   *Do not touch the spike tip of the access device at any time.*





3. Place vial on a hard surface. With a straight push down movement press the spike tip of the vial access device through the centre of the vial's rubber stopper until the device securely snaps onto the vial top.



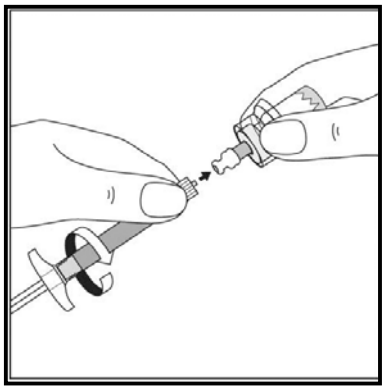
4. Swab the connection point of the vial access device with preferred antiseptic prior to attaching the syringe to the vial access device.

5. Open the prefilled syringe by breaking the seal of the closure and remove the white cap together with the rubber tip cap inside.

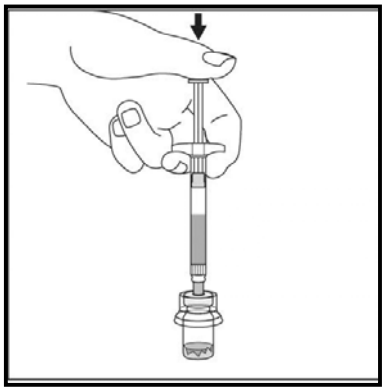

6. Press the syringe tip into the vial access device and twist in a clockwise motion to ensure that the syringe is securely attached to the white luer cap of the vial access device.

   Hold the skirt of the vial access device during attachment to prevent spinning.

   *Keep the syringe and the vial access device aligned.*

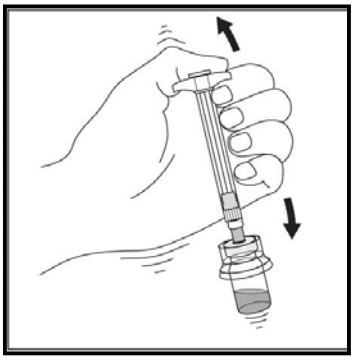


7. Inject the entire contents (solvent) of the syringe into the vial.



8. Holding the plunger rod down with the thumb, shake the vial vigorously for at least 10 seconds until obtaining a homogeneous suspension.

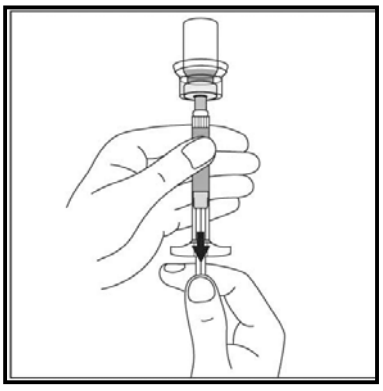
   Mixing is complete when the suspension appears uniform, thick, and milky in colour and all the powder is fully dispersed.



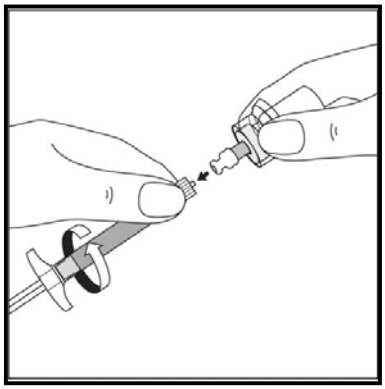
**DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.**

9. Invert the vial completely and slowly withdraw the entire contents of the suspension from the vial.

   For identification purposes, tear section of the vial label at the perforation and apply detached section to the syringe.

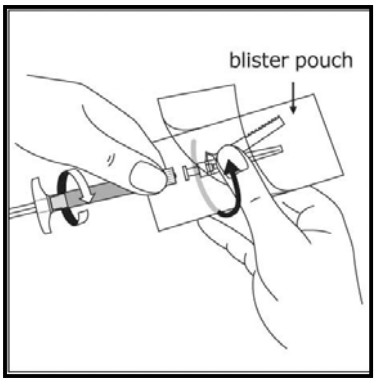


10. Unscrew the syringe from the vial access device. Discard the vial and the vial access device appropriately.



11. Peel the blister pouch of the Needle-Pro device open half way. Grasp sheath using the plastic peel pouch.
Attach the luer connection of the Needle-Pro device with an easy clockwise twisting motion to the syringe. Seat the needle firmly on the Needle-Pro device with a push and clockwise twist.

*Prepare the patient for injection.*



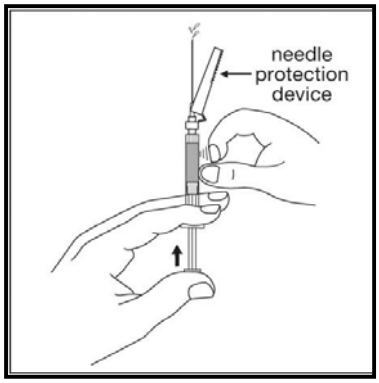

**RESUSPENSION OF RISPERDAL CONSTA WILL BE NECESSARY PRIOR TO ADMINISTRATION AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSPHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.**

12. Pull sheath away from the needle – do not twist sheath as needle may be loosened from Needle-Pro device.

Tap the syringe gently to make any air bubbles rise to the top.

Remove air bubbles from the syringe barrel by moving the plunger rod forward with the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the buttock of the patient.

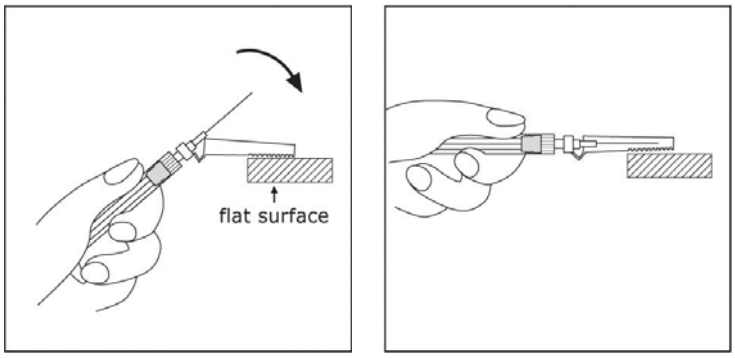
**DO NOT ADMINISTER INTRAVENOUSLY.**



**WARNING:** To avoid a needle stick injury with a contaminated needle, do not :

- Intentionally disengage the Needle-Pro device
- Attempt to straighten the needle or engage the Needle-Pro device if the needle is bent or damaged
- Mishandle the needle protection device that could lead to protrusion of the needle from it

13. After procedure is completed, press the needle into the needle protection device. Perform a one-handed technique by GENTLY pressing the needle protection device against a flat surface. As the needle protection device is pressed, the needle is firmly engaged into it. Visually confirm that the needle is fully engaged into the needle protection device. Immediately discard appropriately.




Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I – To be completed nationally]

{Name and address}

## 8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

## 10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

# LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Outer Carton (Pack with ALARIS)

**1. NAME OF THE MEDICINAL PRODUCT**

RISPERDAL CONSTA and associated names (see Annex I) 12.5 mg powder and solvent for prolonged-release suspension for intramuscular injection
[See Annex I – To be completed nationally]

RISPERDAL CONSTA and associated names (see Annex I) 25 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 37.5 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 50 mg powder and solvent for prolonged-release suspension for intramuscular injection

risperidone

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

[To be completed nationally]

**3. LIST OF EXCIPIENTS**

[To be completed nationally]

**4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for prolonged-release suspension for injection.

[To be completed nationally]

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
For intramuscular use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

[To be completed nationally]

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and Address}

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Outer Carton (Pack with 3 needle system)

## 1. NAME OF THE MEDICINAL PRODUCT

RISPERDAL CONSTA and associated names (see Annex I) 12.5 mg powder and solvent for prolonged-release suspension for intramuscular injection
[See Annex I – To be completed nationally]

RISPERDAL CONSTA and associated names (see Annex I) 25 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 37.5 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 50 mg powder and solvent for prolonged-release suspension for intramuscular injection

risperidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

## 3. LIST OF EXCIPIENTS

[To be completed nationally]

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.

[To be completed nationally]

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intramuscular use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

[To be completed nationally]

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and Address}

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

Outer Carton (Pack with ALARIS and separate storage for solvent)

## 1. NAME OF THE MEDICINAL PRODUCT

RISPERDAL CONSTA and associated names (see Annex I) 12.5 mg powder and solvent for prolonged-release suspension for intramuscular injection
[See Annex I – To be completed nationally]

RISPERDAL CONSTA and associated names (see Annex I) 25 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 37.5 mg powder and solvent for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 50 mg powder and solvent for prolonged-release suspension for intramuscular injection

risperidone

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

[To be completed nationally]

## 3. LIST OF EXCIPIENTS

[To be completed nationally]

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for prolonged-release suspension for injection.

[To be completed nationally]

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intramuscular use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

[To be completed nationally]

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and Address}

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Batch

**14. GENERAL CLASSIFICATION FOR SUPPLY**

[To be completed nationally]

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Vial for powder for suspension for injection (all packs)**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RISPERDAL CONSTA and associated names (see Annex I) 12.5 mg powder for prolonged-release suspension for intramuscular injection
[See Annex I – To be completed nationally]

RISPERDAL CONSTA and associated names (see Annex I) 25 mg powder for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 37.5 mg powder for prolonged-release suspension for intramuscular injection

RISPERDAL CONSTA and associated names (see Annex I) 50 mg powder for prolonged-release suspension for intramuscular injection

risperidone

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

## 6. OTHER

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**Pre filled Syringe (all packs)**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for RISPERDAL CONSTA 12.5 mg/25 mg/37.5 mg/50 mg and associated names (see Annex I)
[See Annex I – To be completed nationally]

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Batch

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

[To be completed nationally]

## 6. OTHER

Keep prefilled syringe in the outer carton

**PACKAGE LEAFLET**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**RISPERDAL CONSTA and associated names (see Annex I) 12.5, 25, 37.5 and 50 mg powder and solvent for prolonged-release suspension for intramuscular injection**

[See Annex I – To be completed nationally]

Risperidone

**Read all of this leaflet carefully before you start using this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:


1. What RISPERDAL CONSTA is and what it is used for
2. Before you use RISPERDAL CONSTA
3. How to use RISPERDAL CONSTA
4. Possible side effects
5. How to store RISPERDAL CONSTA
6. Further information


## 1. WHAT RISPERDAL CONSTA IS AND WHAT IT IS USED FOR

RISPERDAL CONSTA belongs to a group of medicines called ‘anti-psychotics’.

RISPERDAL CONSTA is used to maintain the treatment of schizophrenia, where you may see, hear or feel things that are not there, believe things that are not true or feel unusually suspicious, or confused

RISPERDAL CONSTA is intended for patients who are currently treated with oral (e.g. tablets, capsules) antipsychotics.

## 2. BEFORE YOU USE RISPERDAL CONSTA

**Do not take RISPERDAL CONSTA**

- If you are allergic (hypersensitive) to risperidone or any of the other ingredients of RISPERDAL CONSTA (listed in Section 6 below).

**Take special care with RISPERDAL CONSTA**

- If you have never taken any form of RISPERDAL, you should begin with oral RISPERDAL before beginning treatment with RISPERDAL CONSTA.

Check with your doctor or pharmacist before using RISPERDAL CONSTA if:

- You have a heart problem. Examples include an irregular heart rhythm or if you are prone to low blood pressure or if you are using medicines for your blood pressure. RISPERDAL CONSTA may cause low blood pressure. Your dose may need to be adjusted.
- You know of any factors which would favour you having a stroke, such as high blood pressure, cardiovascular disorder or circulation disorders of the brain
- You have Parkinson’s disease or dementia
- You are diabetic
- You have epilepsy

- You are a man and have ever had a prolonged or painful erection. If you experience this while taking RISPERDAL CONSTA, contact your doctor straight away
- You have difficulty controlling body temperature or overheating
- You have kidney problems
- You have liver problems
- You have an abnormally high level of the hormone prolactin in your blood or if you have a tumour, which is possibly dependent on prolactin.

**Tell your doctor immediately if you experience**

- involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of risperidone may be needed
- fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome). Immediate medical treatment may be needed.

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using RISPERDAL or RISPERDAL CONSTA.

RISPERDAL CONSTA may cause you to gain weight.

**Elderly people with dementia**
RISPERDAL CONSTA is not for use in elderly people with dementia.

Medical treatment should be sought straight away if you or your carer notice a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.

**Using other medicines**
Please tell your doctor or pharmacist if you are using or have recently used any other medicines, including medicines obtained without a prescription and herbal medicines.

It is especially important to talk to your doctor or pharmacist if you are taking any of the following:
- Medicines that work on your brain to help you calm down (benzodiazepines), or some medicines for pain (opiates), medicines for allergy (some antihistamines), as Risperidone may increase the sedative effect of all of these.
- Medicines that may change the electrical activity of your heart, such as medicines for malaria, heart rhythm problems (such as quinidine), allergies (anti-histamines), some antidepressants or other medicines for mental problems
- Medicines that cause a slow heart beat
- Medicines that cause low blood potassium (e.g. certain diuretics)
- Medicines for Parkinson's disease (such as levodopa)
- Medicines to treat elevated blood pressure. RISPERDAL CONSTA can lower blood pressure
- Water tablets (diuretics) used for heart problems or swelling of parts of your body due to a build up of too much fluid (such as furosemide or chlorothiazide). RISPERDAL CONSTA taken by itself or with furosemide, may have an increased risk of stroke or death in elderly people with dementia.

The following medicines may reduce the effect of risperidone
- Rifampicin (a medicine for treating some infections)
- Carbamazepine, phenytoin (mdicines for epilepsy)
- Phenobarbital

If you start or stop taking such medicines you may need a different dose of risperidone

The following medicines may increase the effect of risperidone
- Quinidine (used for certain types of heart disease)

- Antidepressants such as paroxetine, fluoxetines, tricyclic antidepressants
- Medicines known as beta blockers (used to treat high blood pressure)
- Phenothiazines (e.g. used to treat psychosis or to calm down)
- Cimetidie, ranitidine (blockers of the acidity of stomach)

If you start or stop taking such medicines you may need a different dose of risperidone

If you are not sure if any of the above applies to you, talk to your doctor or pharmacist before using RISPERDAL CONSTA.

**Using RISPERDAL CONSTA with food and drink**
You should avoid drinking alcohol when using RISPERDAL CONSTA.

**Pregnancy and breast-feeding**
- Talk to your doctor before using RISPERDAL CONSTA if you are pregnant, trying to become pregnant or breast-feeding. Your doctor will decide if you can use it
- Shaking, muscle stiffness and problems feeding, all of which are reversible, have been seen in newborn babies when RISPERDAL was used during the last trimester of pregnancy.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**
Dizziness, tiredness, and vision problems may occur during treatment with RISPERDAL CONSTA. Do not drive or use any tools or machines without talking to your doctor first.

## 3. HOW TO USE RISPERDAL CONSTA

RISPERDAL CONSTA is given as an intramuscular injection into the buttocks every two weeks, administered by a health care professional.

**Adults**
Starting dose
If your daily dose of oral (e.g. tablets) risperidone was 4 mg or less for the last two weeks, your starting dose should be 25 mg RISPERDAL CONSTA.
If your daily dose of oral (e.g. tablets) risperidone was more than 4 mg for the last two weeks, you may be given 37.5 mg RISPERDAL CONSTA as a starting dose.

If you are currently treated with other oral antipsychotics than risperidone, your starting dose of RISPERDAL CONSTA will depend on your current treatment. Your doctor will choose RISPERDAL CONSTA 25 mg or 37.5 mg.

You may be given a lower dose of 12.5 mg. Your doctor will decide on the dose of RISPERDAL CONSTA that is right for you.

Maintenance dose
- The usual dose is 25 mg every two weeks as an injection
- A lower dose of 12.5 mg or a higher dose of 37.5 or 50 mg may also be necessary. Your doctor will decide on the dose of RISPERDAL CONSTA that is right for you
- Your doctor may prescribe oral RISPERDAL for the first three weeks following your first injection.

**Children and adolescents**
RISPERDAL CONSTA is not for people who are under 18 years old.

**If you are given more RISPERDAL CONSTA than you should**

- People who have been given more RISPERDAL CONSTA than they should have experienced the following symptoms: sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats. Cases of abnormal electrical conduction in the heart and convulsion have been reported
- See a doctor right away.

**If you stop using RISPERDAL CONSTA**
You will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return. Be sure not to miss your appointments when you are supposed to receive your injections every two weeks. If you cannot keep your appointment, be sure to contact your doctor right away to discuss another date when you can come in for your injection. If you have any further questions on the use of this product, ask your doctor or pharmacist.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, RISPERDAL CONSTA can cause side effects, although not everybody gets them.

| | |
|---|---|
| Very common: | affects more than 1 user in 10 |
| Common: | affects 1 to 10 users in 100 |
| Uncommon: | affects 1 to 10 users in 1,000 |
| Rare: | affects 1 to 10 users in 10,000 |
| Very rare: | affects less than 1 user in 10,000 |
| Not known: | frequency cannot be estimated from the available data. |

The following side effects may happen:
**Very common side effects (affects more than 1 user in 10):**
- Inability to sleep, anxiety, depression, irritability, feeling of inner restlessness
- Headache, nose and throat infection
- Parkinsonism. This is a medical term that includes many symptoms. Each individual symptom may occur less frequently than in 1 in 10 people. Parkinsonism includes: increase in saliva secretion or watery mouth, musculoskeletal stiffness, drooling, jerks when bending the limbs, slow, reduced or impaired body movements, no expression on the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex).

**Common side effects (affects 1 to 10 users in 100):**
- Restlessness, sleep disorder, dizziness, feeling dizzy when staying still, fatigue, drowsiness, sleepiness
- Weight increased, toothache, weight decreased
- Vomiting, diarrhea, constipation, nausea, dry mouth, abdominal pain or stomach discomfort, stomach infection
- Difficulty breathing, lung infection (pneumonia), flu, infection of the breathing passages, urinary tract infection, increase in body temperature, urinary incontinence, sinus infection, viral infection, ear infection, nose congestion, sore throat, ‘pink eye’, flu-like illness, cough
- Blurred vision
- Tremor, muscle weakness, fall, back pain, muscle spasm, pain in arms and legs, joint pain, involuntary movement of face or limb muscles, muscle pain, swelling of the arms and legs
- Blood prolactin hormone level increased, liver enzymes increased, decrease in hemoglobin or red blood cell count (anemia), blood sugar increased
- No menstruation, erectile dysfunction, breast discharge
- Abnormal electrical conduction of the heart, high blood pressure, fast beating heart, chest pain, low blood pressure, abnormal electrical tracing of the heart (ECG)
- Rash, injection site pain, skin redness.

**Uncommon side effects (affects 1 to 10 users in 1000):**

- Nervousness, poor attention, feeling very sleepy, exhausted, or weary, excessive sleep, elated mood (mania), feeling 'out of sorts', sluggishness
- Nasal congestion
- Bladder infection, stomach and intestine infection, ear pain
- Sudden swelling of lips and eyes along with difficulty breathing, allergy
- Neck pain, buttock pain, musculoskeletal chest pain, pain during injection procedure, chest discomfort, swelling and thickening of skin at injection site
- Decreased appetite, increased appetite
- Sexual dysfunction, enlargement of breast in men, decreased sexual drive
- Intense itching of the skin, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin, abscess under the skin, hair loss, acne, dry skin
- Fainting, drop in blood pressure after standing, feeling dizzy after changing body position
- Abnormal heart rhythm, awareness of heart beating, slow beating heart,
- Body shakes rapidly and uncontrollably (convulsion)
- Decrease in white blood cells that help against infection, decrease in platelets (blood cells that help you stop bleeding).

**Rare side effects (affects 1 to 10 users in 10,000):**

- Trouble breathing during sleep
- Obstruction of intestine
- Yellowing of the skin and the eyes (jaundice)
- Inappropriate secretion of a hormone that controls urine volume
- Inflammation of the pancreas.

**Very rare side effects (affects less than 1 user in 10,000) may include:**

- Life-threatening complications of uncontrolled diabetes.

**Unknown frequency of occurrence (frequency cannot be estimated from the available data):**

- Severe allergic reaction resulting in difficulty in breathing and shock
- No granulocytes (a type of white blood cell to help you against infection)
- Prolonged and painful erection
- Dangerously excessive intake of water
- Sudden loss of vision or blindness.

**RISPERDAL Oral**

The following side effects have been reported with the use of RISPERDAL Oral. Even if you are not being treated with RISPERDAL Oral but you experience any of the following, talk to your doctor:

- Bed wetting, difficulty in urination, urination at short intervals, vaginal discharge
- Tonsillitis, eye infection, skin infection, fungal infection of nails
- Lack of emotion, confusion, poor attention, loss of consciousness, balance disorder
- Unresponsive to stimuli, stroke, decreased blood supply to the brain, brain blood vessel disorder, sudden weakness or numbness of the face, arms, or legs, especially on one side, or instances of slurred speech that last for less than 24 hours (these are called mini-strokes or strokes)
- Eye discharge, eye rolling, eye swelling, ringing in the ears, nose bleeding, dry eye, increased tears, painful oversensitivity to light, increased pressure within the eyeball, reduced visual clarity
- Wheezing, pneumonia caused by inhaling food, hoarseness, cough with sputum, lung congestion, breathing passage congestion, crackly lung noise, breathing passage disorder, fast shallow breathing
- Very hard feces, fecal incontinence, abdominal discomfort, thirst, lip swelling, inflammation of the colon, reduced saliva
- Skin discoloration, skin lesion, skin disorder, thickening of the skin

- Abnormal posture, joint stiffness, neck pain, breakdown of muscle and pain in muscles
- Gait disturbance, edema, body temperature increased, drug allergy, speech disorder, movement disorder
- Eosinophil (special white blood cells ) count increased, blood creatine phosphokinase increased
- Inability to reach orgasm, ejaculation disorder, menstrual disorder
- Change in consciousness with increased body temperature and twitching of muscles
- Flushing, oily skin inflammation, dandruff, rash all over the body
- Discomfort, chills, arm or leg coldness, drug withdrawal syndrome.

**If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.**

## 5. HOW TO STORE RISPERDAL CONSTA

[To be completed nationally]

Keep out of the reach and sight of children.

Do not use RISPERDAL CONSTA after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What RISPERDAL CONSTA contains**

[To be completed nationally]

The active substance is risperidone.
Each RISPERDAL CONSTA powder and solvent for prolonged-release suspension for injection contains either 12.5 mg, 25 mg, 37.5 mg or 50 mg of risperidone.

**Solvent (solution)**

[To be completed nationally]

**What RISPERDAL CONSTA looks like and contents of the pack**

[To be completed nationally]

**Marketing Authorisation Holder and Manufacturer**

[See Annex I - To be completed nationally]

{Name and address}

**This medicinal product is authorised in the Member States of the EEA under the following names:**

[To be completed nationally]

Austria: RISPERDAL® CONSTA®
Belgium: RISPERDAL® CONSTA®/ BELIVON® CONSTA®
Bulgaria: РИСПОЛЕПТ КОНСТА™
Cyprus: RISPERDAL® CONSTA®
Czech Republic: RISPERDAL® CONSTA®
Denmark: RISPERDAL® CONSTA®
Estonia: RISPOLEPT® CONSTA®
Finland: RISPERDAL® CONSTA®
France: RISPERDALCONSTA® LP
Germany: RISPERDAL CONSTA / Risperidon-Janssen CONSTA
Greece: RISPERDAL® CONSTA
Hungary: RISPERDAL CONSTA
Iceland: RISPERDAL® CONSTA®
Ireland: RISPERDAL® CONSTA™
Italy: RISPERDAL®
Lithuania: RISPOLEPT® CONSTA®
Latvia: RISPOLEPT® CONSTA®
Liechtenstein: RISPERDAL® CONSTA®
Luxembourg: RISPERDAL® CONSTA® / BELIVON® CONSTA®
Malta: RISPERDAL® CONSTA®
Netherlands: RISPERDAL® CONSTA®
Norway: RISPERDAL® CONSTA®
Poland: RISPOLEPT CONSTA®
Portugal: RISPERDAL® CONSTA®
Romania: RISPOLEPT CONSTA®
Slovakia: RISPERDAL® CONSTA®
Slovenia: RISPERDAL CONSTA®
Spain: RISPERDAL® CONSTA
Sweden: RISPERDAL® CONSTA®
United Kingdom: RISPERDAL® CONSTA®

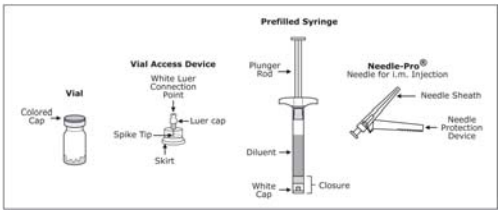
**This leaflet was last approved in** {MM/YYYY}.

[To be completed nationally]

IMPORTANT INFORMATION FOR HEALTHCARE PROFESSIONALS

**Instructions for Needle-Free Vial Access Device**

RISPERDAL CONSTA extended release microspheres in the vial must be reconstituted only in the solvent in the syringesupplied in the dose pack, and must be administered only with the Needle-Pro safety needle supplied in the dose pack. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.

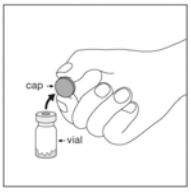



Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature prior to reconstitution.

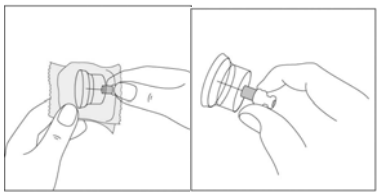
Contents of the dose pack:

- One vial containing RISPERDAL CONSTA extended release microspheres
- One Alaris SmartSite needle-free vial access device for reconstitution
- One prefilled syringe containing 2 ml solvent for RISPERDAL CONSTA
- One Needle-Pro needle for intramuscular injection (safety 20G 2” TW needle-with needle protection device).

1. Flip off the plastic colored cap from the vial




2. Peel back the blister pouch and remove the vial access device by holding the white luer cap. Do not touch the spike tip of the access device at any time.



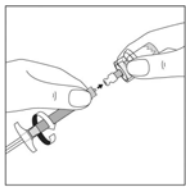
3. Place vial on a hard surface. With a straight push down movement press the spike tip of the vial access device through the center of the vial’s rubber stopper until the device securely snaps onto the vial top.

4. Swab the connection point of the vial access device with preferred antiseptic prior to attaching the syringe to the vial access device.

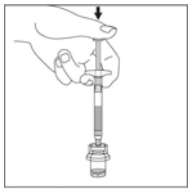
5. Open the prefilled syringe by breaking the seal of the closure and remove the white cap together with the rubber tip cap inside.


6. Press the syringe tip into the vial access device and twist in a clockwise motion to ensure that the syringe is securely attached to the white luer cap of the vial access device.

   Hold the skirt of the vial access device during attachment to prevent spinning.
   Keep the syringe and the vial access device aligned.

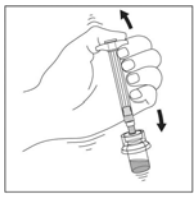


7. Inject the entire contents (solvent) of the syringe into the vial.



8. Holding the plunger rod down with the thumb, shake the vial vigorously for at least 10 seconds until obtaining a homogeneous suspension.

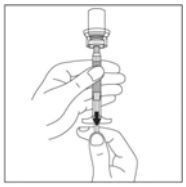
   Mixing is complete when the suspension appears uniform, thick, and milky in color and all the powder is fully dispersed.



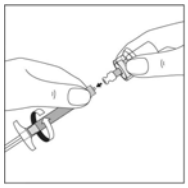
DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE.

9. Invert the vial completely and slowly withdraw the entire contents of the suspension from the vial.

   For identification purposes, tear section of the vial label at the perforation and apply detached section to the syringe.

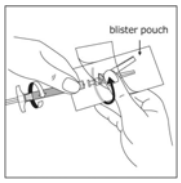


10. Unscrew the syringe from the vial access device. Discard the vial and the vial access device appropriately.



11. Peel the blister pouch of the Needle-Pro device open half way. Grasp sheath using the plastic peel pouch.

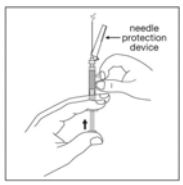
    Attach the luer connection of the Needle-Pro device with an easy clockwise twisting motion to the syringe. Seat the needle firmly on the Needle-Pro device with a push and clockwise twist. Prepare the patient for injection.




RESUSPENSION OF RISPERDAL CONSTA WILL BE NECESSARY PRIOR TO ADMINISTRATION AS SETTLING WILL OCCUR OVER TIME ONCE PRODUCT IS RECONSTITUTED. RESUSPEND THE MICROSPHERES IN THE SYRINGE BY SHAKING VIGOROUSLY.

12. Pull sheath away from the needle -do not twist sheath as needle may be loosened from Needle-Pro device.

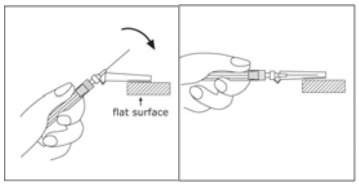
    Tap the syringe gently to make any air bubbles rise to the top.
    Remove air bubbles from the syringe barrel by moving the plunger rod forward with the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the buttock of the patient.
    DO NOT ADMINISTER INTRAVENOUSLY.




**WARNING: To avoid a needle stick injury with a contaminated needle, do not :**

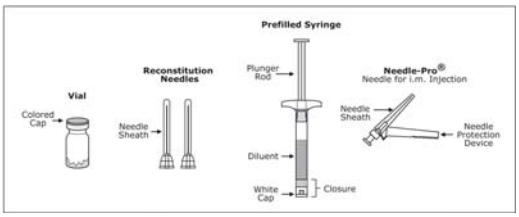
- **Intentionally disengage the Needle-Pro device**
- **Attempt to straighten the needle or engage the Needle-Pro device if the needle is bent or damaged**
- **Mishandle the needle protection device that could lead to protrusion of the needle from it.**

13. After procedure is completed, press the needle into the needle protection device. Perform a one-handed technique by GENTLY pressing the needle protection device against a flat surface. As the needle protection device is pressed, the needle is firmly engaged into it. Visually confirm that the needle is fully engaged into the needle protection device. Immediately discard appropriately.




**Instructions for Three Needle System**

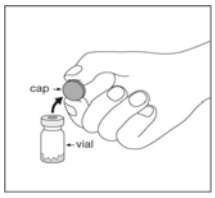
RISPERDAL CONSTA come in a form of a powder that must be mixed with **only** the solution in the syringe supplied in the dose pack, and must be administered **only** with the Needle-Pro safety needle supplied in the dose pack. Do not substitute any components in the dose pack. To assure that the intended dose of risperidone is delivered, the full contents from the vial must be administered. Administration of partial contents may not deliver the intended dose of risperidone.



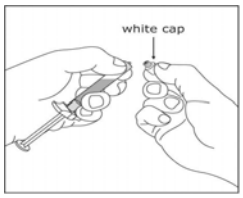

Remove the dose pack of RISPERDAL CONSTA from the refrigerator and allow it to come to room temperature prior to reconstitution.
Contents of the dose pack:

- One vial containing RISPERDAL CONSTA extended release microspheres
- Two Hypoint 20G 2” TW needles for reconstitution
- One prefilled syringe containing 2 ml solvent for RISPERDAL CONSTA
- One Needle-Pro needle for intramuscular injection (safety 20G 2” TW needle with needle protection device).

1. Flip off the plastic colored cap from the vial

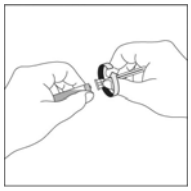



2. Open the prefilled syringe by breaking the seal of the closure and remove the white cap together with the rubber tip cap inside




3 Open the cover of one reconstitution needle.

*Keeping the syringe and needle aligned,* attach the needle with an easy clockwise twisting motion to the luer connection of the syringe.



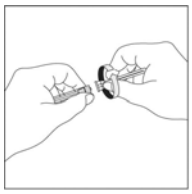
4. Pull sheath away from the needle - do not twist.

   Inject the entire contents (solvent) of the syringe into the vial

5. Withdraw the syringe with the reconstitution needle from the vial. Unscrew the needle from the syringe and discard the needle appropriately.

6. Open the cover of the second reconstitution needle.

   *Keeping the empty syringe and needle aligned,* attach the second needle with an easy clockwise twisting motion to the luer connection of the syringe.
   Do not remove the sheath from the needle at this time.



7. Shake the vial vigorously for at least 10 seconds until obtaining a homogeneous suspension.

   Mixing is complete when the suspension appears uniform, thick, and milky in color, and all the powder is fully dispersed.

   DO NOT STORE THE VIAL AFTER RECONSTITUTION OR THE SUSPENSION MAY SETTLE

8. Take the syringe and pull sheath away from the reconstitution needle - donot twist.

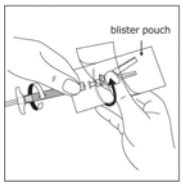
   Insert the reconstitution needle into the upright vial.
   Slowly withdraw the suspension from the vial in an upright, but slightly angled position as indicated in the picture to ensure that the entire contents are drawn up into the syringe

9. Withdraw the syringe with the reconstitution needle from the vial. Unscrew the needle from the syringe and discard the needle appropriately.

   For identification purposes, tear section of the vial label at the perforation and apply detached section to the syringe. Discard the vial appropriately.

10. Peel the blister pouch of the Needle-Pro device open half way. Grasp sheath using the plastic peel pouch.

    Attach the luer connection of the Needle-Pro device with an easy clockwise twisting motion to the syringe. Seat the needle firmly on the Needle-Pro device with a push and clockwise twist. Prepare the patient for injection

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11. Pull sheath away from the needle - do not twist sheath as needle may be loosened from Needle-Pro® device.

    Tap the syringe gently to make any air bubbles rise to the top.
    Remove air bubbles from the syringe barrel by moving the plunger rod forward with the needle in an upright position. Inject the entire contents of the syringe intramuscularly into the buttock of the patient.
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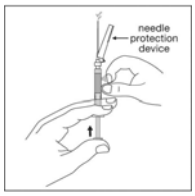


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that the needle is fully engaged into the needle protection device. Immediately discard appropriately.