

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION
HOLDERS IN THE MEMBER STATES (EU/EEA)**

Marketing Authorisations for medicinal products containing METHYLPHENIDATE

| Member State (EU/EEA) | Marketing Authorisation Holder | Invented Name | Strength | Pharmaceutical form | Route of administration |
|------------------------------|---|--|-----------------|------------------------------------|--------------------------------|
| AT - Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien | Concerta 18 mg Retardtabletten | 18 mg | Prolonged-release tablet | oral use |
| AT - Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien | Concerta 36 mg Retardtabletten | 36 mg | Prolonged-release tablet | oral use |
| AT - Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien | Concerta 54 mg Retardtabletten | 54 mg | Prolonged-release tablet | oral use |
| AT - Austria | Janssen-Cilag Pharma GmbH Pfarrgasse 75 A-1232 Wien | Concerta 27 mg Retardtabletten | 27 mg | Prolonged-release tablet | oral use |
| AT - Austria | UCB Pharma GmbH Jauringasse 16-18/3 A-1030 Wien | Equasym retard 10 mg - Hartkapseln mit veränderter Wirkstofffreisetzung | 10 mg | Modified-release capsule, hard | oral use |
| AT - Austria | UCB Pharma GmbH Jauringasse 16-18/3 A-1030 Wien | Equasym retard 20 mg - Hartkapseln mit veränderter Wirkstofffreisetzung | 20 mg | Modified-release capsule, hard | oral use |
| AT - Austria | UCB Pharma GmbH Jauringasse 16-18/3 A-1030 Wien | Equasym retard 30 mg - Hartkapseln mit veränderter Wirkstofffreisetzung | 30 mg | Modified-release capsule, hard | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 10 mg - retardierte Hartkapseln | 10 mg | Prolonged-release capsule, hard | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 20 mg - retardierte Hartkapseln | 20 mg | Prolonged-release capsule, hard | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 30 mg - retardierte Hartkapseln | 30 mg | Prolonged-release capsule, hard | oral use |

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|--------------|---|---|-------|---------------------------------|----------|
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 40 mg - retardierte Hartkapseln | 40 mg | Prolonged-release capsule, hard | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 5 mg - Tabletten | 5 mg | tablet | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 10 mg - Tabletten | 10 mg | tablet | oral use |
| AT - Austria | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 DE-58638 Iserlohn | Medikinet 20 mg - Tabletten | 20 mg | tablet | oral use |
| AT - Austria | Novartis Pharma GmbH Brunner Straße 59 A-1235 Wien | Ritalin LA 20 mg - Kapseln | 20 mg | Modified-release capsule, hard | oral use |
| AT - Austria | Novartis Pharma GmbH Brunner Straße 59 A-1235 Wien | Ritalin LA 30 mg - Kapseln | 30 mg | Modified-release capsule, hard | oral use |
| AT - Austria | Novartis Pharma GmbH Brunner Straße 59 A-1235 Wien | Ritalin LA 40 mg - Kapseln | 40 mg | Modified-release capsule, hard | oral use |
| AT - Austria | Novartis Pharma GmbH Brunner Straße 59 A-1235 Wien | Ritalin 10 mg - Tabletten | 10 mg | tablet | oral use |
| AT - Austria | Laboratorios Rubio SA C/Industria 29, Poligon Industrial Compte de Sert ES-08755 Castellbisbal (Barcelona) | RUBIFEN 5 mg -Tabletten | 5 mg | tablet | oral use |
| AT - Austria | Laboratorios Rubio SA C/Industria 29, Poligon Industrial Compte de Sert ES-08755 Castellbisbal (Barcelona) | RUBIFEN 10 mg -Tabletten | 10 mg | tablet | oral use |
| AT - Austria | Laboratorios Rubio SA C/Industria 29, Poligon Industrial Compte de Sert ES-08755 Castellbisbal (Barcelona) | RUBIFEN 20 mg -Tabletten | 20 mg | tablet | oral use |
| BE - Belgium | JANSSEN CILAG N.V. Roderveldlaan, 1 B-2600 BERCHEM | CONCERTA 18 MG | 18 mg | Prolonged-release tablet | oral use |

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| BE - Belgium | JANSSEN CILAG N.V. Roderveldlaan, 1 B-2600 BERCHEM | CONCERTA 36 MG | 36 mg | Prolonged-release tablet | oral use |
| BE - Belgium | JANSSEN CILAG N.V. Roderveldlaan, 1 B-2600 BERCHEM | CONCERTA 54 MG | 54 mg | Prolonged-release tablet | oral use |
| BE - Belgium | JANSSEN CILAG N.V. Roderveldlaan, 1 B-2600 BERCHEM | CONCERTA 27 MG | 27 mg | Prolonged-release tablet | oral use |
| BE - Belgium | NOVARTIS PHARMA N.V. Medialaan, 40 1800 VILVOORDE | RILATINE | 10 mg | tablet | oral use |
| BE - Belgium | NOVARTIS PHARMA N.V. Medialaan, 40 1800 VILVOORDE | RILATINE MODIFIED RELEASE 20 MG | 20 mg | Modified-release capsule, hard | oral use |
| BE - Belgium | NOVARTIS PHARMA N.V. Medialaan, 40 1800 VILVOORDE | RILATINE MODIFIED RELEASE 30 MG | 30 mg | Modified-release capsule, hard | oral use |
| BE - Belgium | NOVARTIS PHARMA N.V. Medialaan, 40 1800 VILVOORDE | RILATINE MODIFIED RELEASE 40 MG | 40 mg | Modified-release capsule, hard | oral use |
| BG - Bulgaria | Johnson & Johnson D.O.O. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta | 36 mg | prolonged release tablet | Oral use |
| BG - Bulgaria | Johnson & Johnson D.O.O. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta | 18 mg | prolonged release tablet | Oral use |
| BG - Bulgaria | Johnson & Johnson D.O.O. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta | 54 mg | prolonged release tablet | Oral use |

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| CY - Cyprus | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta | 18 mg | prolonged-release tablet | oral use |
| CY - Cyprus | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta | 36 mg | prolonged-release tablet | oral use |
| CY - Cyprus | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta | 54 mg | prolonged-release tablet | oral use |
| CS - Czech Republic | Novartis s.r.o. Nagano III. U Nákladového nádraží 10 130 00 Praha 3, Czech Republic | RITALIN | 10 mg | tablet | oral use |
| CS – Czech Republic | Janssen-Cilag s.r.o., Karla Engliš 3201/6, 150 00 Praha 5 – Smíchov, Czech Republic | CONCERTA 18 mg | 18 mg | prolonged release tablet | oral use |
| CS – Czech Republic | Janssen-Cilag s.r.o., Karla Engliš 3201/6, 150 00 Praha 5 – Smíchov, Czech Republic | CONCERTA 36 mg | 36 mg | prolonged release tablet | oral use |
| CS – Czech Republic | Janssen-Cilag s.r.o., Karla Engliš 3201/6, 150 00 Praha 5 – Smíchov, Czech Republic | CONCERTA 54 mg | 54 mg | prolonged release tablet | oral use |
| DK - Denmark | Janssen-Cilag A/S Hammerbakken 19 DK-3460 Birkerød Denmark | CONCERTA | 18 mg | Prolonged-release tablets | Oral use |
| DK-Denmark | Janssen-Cilag A/S Hammerbakken 19 DK-3460 Birkerød Denmark | CONCERTA | 36 mg | Prolonged-release tablets | Oral use |

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|--------------|--|---------------|----------------------|---------------------------------|----------|
| DK - Denmark | Janssen-Cilag A/S Hammerbakken 19 DK-3460 Birkerød Denmark | CONCERTA | 54 mg | Prolonged-release tablets | Oral use |
| DK - Denmark | UCB Nordic A/S Arne Jacobsen Allé 15, DK-2300 København S Denmark | Equasym | 5 mg | Tablets | Oral |
| DK - Denmark | UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 København S Denmark | Equasym | 10 mg | Tablets | Oral |
| DK - Denmark | UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 København S Denmark | Equasym | 20 mg | Tablets | Oral |
| DK - Denmark | UCB Nordic A/S Arne Jacobsen Allé 15, DK-2300 København S Denmark | Equasym Depot | 10, 20, 30 mg | Modified-release capsules, hard | Oral |
| DA | Medice Arzneimittel Kuhloweg 37-39 Iserlohn Germany | Medikinet | 5, 10, 20 mg | Tablets | Oral |
| DA | Medice Arzneimittel Kuhloweg 37-39 Iserlohn Germany | Medikinet CR | 10, 20, 30, 40 mg | Hard capsules, modified release | Oral |
| DA | Sandoz A/S C.F. Tietgens Boulevard 40 5220 Odense SØ Denmark | Motiron | 5, 10, 20 mg | Tablets | Oral |

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|------------|--|--|------------------|---------------------------------|----------|
| DA | Novartis Healthcare Lyngbyvej 172 2100 København Ø Denmark | Ritalin | 10 mg | Tablets | Oral |
| DA | Novartis Healthcare Lyngbyvej 172 2100 København Ø Denmark | Ritalin Uno | 20, 30, 40 mg | Hard capsules, modified release | oral |
| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | RUBIFEN 10 mg comprimidos | 10 mg | tablets | oral use |
| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | RUBIFEN 20 mg comprimidos | 20 mg | tablets | oral use |
| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | RUBIFEN 5 mg comprimidos | 5 mg | tablets | oral use |
| ES - Spain | JANSSEN CILAG, SA Paseo de las doce estrellas, 5-7 Madrid 28042 | CONCERTA 27 mg comprimidos de liberación prolongada | 27 mg | prolonged-release tablet | oral use |
| ES - Spain | JANSSEN CILAG, SA Paseo de las doce estrellas, 5-7 Madrid 28042 | CONCERTA 36 mg comprimidos de liberación prolongada | 36 mg | prolonged-release tablet | oral use |
| ES - Spain | JANSSEN CILAG, SA Paseo de las doce estrellas, 5-7 Madrid 28042 | CONCERTA 54 mg comprimidos de liberación prolongada | 54 mg | prolonged-release tablet | oral use |
| ES - Spain | JANSEN CILANG, SA Paseo de las doce estrellas, 5-7 Madrid 28042 | CONCERTA 18 mg comprimidos de liberación prolongada | 18 mg | prolonged-release tablet | oral use |
| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | OMOZIN 5 mg comprimidos | 5 mg | tablets | oral use |

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| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | OMOZIN 10 mg comprimidos | 10 mg | tablets | oral use |
| ES - Spain | Laboratorios RUBIO, SA Industria 29- Polígono industrial Comte de Sert Castellbisbal 08755 | OMOZIN 20 mg comprimidos | 20 mg | tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 5 mg comprimidos | 5mg | Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 10 mg comprimidos | 10 mg | Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 20 mg comprimidos | 20 mg | Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 10 mg cápsulas de liberación prolongada | 10 mg | prolonged release Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 20 mg cápsulas liberación prlongada | 20 mg | prolonged release Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 30 mg cápsulas liberación prolongada | 30 mg | Prolonged release Tablets | oral use |
| ES - Spain | Medice Arzneimittel Putter GMBH Kuhloweg, 37 D 58638 Iselohon | MEDIKINET 40 mg cápsulas liberación prolongada | 40 mg | Prolonged release Tablets | oral use |
| ET – Estonia | Johnson & Johnson UAB, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 18 mg | prolonged release tablet | oral use |
| ET – Estonia | Johnson & Johnson UAB, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 36 mg | prolonged release tablet | oral use |

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| ET – Estonia | Johnson & Johnson UAB, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 54 mg | prolonged release tablet | oral use |
| FI - Finland | Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo FINLAND | Concerta | 18 mg | prolonged-release tablet | oral |
| FI - Finland | Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo FINLAND | Concerta | 27 mg | prolonged-release tablet | oral |
| FI - Finland | Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo FINLAND | Concerta | 36 mg | prolonged-release tablet | oral |
| FI - Finland | Janssen-Cilag Oy Metsänneidonkuja 8 02130 Espoo FINLAND | Concerta | 54 mg | prolonged-release tablet | oral |
| FI - Finland | UCB Pharma Oy Finland Malminkaari 5 00700 Helsinki FINLAND | Equasym Retard | 10 mg | Modified-release capsule, hard | oral |
| FI - Finland | UCB Pharma Oy Finland Malminkaari 5 00700 Helsinki FINLAND | Equasym Retard | 20 mg | Modified-release capsule, hard | oral |
| FI - Finland | UCB Pharma Oy Finland Malminkaari 5 00700 Helsinki FINLAND | Equasym Retard | 30 mg | Modified-release capsule, hard | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet | 5 mg | tablet | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet | 10 mg | tablet | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet | 20 mg | tablet | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet CR | 10 mg | prolonged-release capsule, hard | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet CR | 20 mg | prolonged-release capsule, hard | oral |

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| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet CR | 30 mg | prolonged-release capsule, hard | oral |
| FI - Finland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 ISERLOHN GERMANY | Medikinet CR | 40 mg | prolonged-release capsule, hard | oral |
| FR - France | JANSSEN CILAG S.A. 1 rue Camille Desmoulins TSA 91003 92787 Issy-les-Moulineaux Cedex 9 France | CONCERTA LP | 18mg | prolonged-release tablet | oral |
| FR - France | JANSSEN CILAG S.A. 1 rue Camille Desmoulins TSA 91003 92787 Issy-les-Moulineaux Cedex 9 France | CONCERTA LP | 27mg | prolonged-release tablet | oral |
| FR - France | JANSSEN CILAG S.A. 1 rue Camille Desmoulins TSA 91003 92787 Issy-les-Moulineaux Cedex 9 France | CONCERTA LP | 36mg | prolonged-release tablet | oral |
| FR - France | JANSSEN CILAG S.A. 1 rue Camille Desmoulins TSA 91003 92787 Issy-les-Moulineaux Cedex 9 France | CONCERTA LP | 54mg | prolonged-release tablet | oral |

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| FR - France | Laboratorios RUBIO SA c/ Industria 29, Pol.Ind.Comte de Sert 08755 Castellbisbal Barcelona SPAIN | METHYLPHENIDATE RUBIO | 10mg | tablet | oral |
| FR - France | Laboratorios RUBIO SA c/ Industria 29, Pol.Ind.Comte de Sert 08755 Castellbisbal Barcelona SPAIN | METHYLPHENIDATE RUBIO | 20mg | tablet | oral |
| FR - France | Laboratorios RUBIO SA c/ Industria 29, Pol.Ind.Comte de Sert 08755 Castellbisbal Barcelona SPAIN | METHYLPHENIDATE RUBIO | 5mg | tablet | oral |
| FR - France | UCB PHARMA S.A. 21 rue de Neuilly BP 314 92003 Nanterre France | QUASYM L.P. 10MG, GELULE A LIBERATION MODIFIEE | 10mg | Modified release capsule, hard | oral |
| FR - France | UCB PHARMA S.A. 21 rue de Neuilly BP 314 92003 Nanterre France | QUASYM L.P. 20MG, GELULE A LIBERATION MODIFIEE | 20mg | Modified release capsule, hard | oral |
| FR - France | UCB PHARMA S.A. 21 rue de Neuilly BP 314 92003 Nanterre France | QUASYM L.P. 30MG, GELULE A LIBERATION MODIFIEE | 30mg | Modified release capsule, hard | oral |

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|--------------|---|----------------|------|----------------------------|------|
| FR - France | NOVARTIS PHARMA SAS 2-4 rue Lionel Terray 92500 Rueil-Malmaison France | RITALINE | 10mg | tablet | oral |
| FR - France | NOVARTIS PHARMA SAS 2-4 rue Lionel Terray 92500 Rueil-Malmaison France | RITALINE L.P. | 20mg | modified release capsule | oral |
| FR - France | NOVARTIS PHARMA SAS 2-4 rue Lionel Terray 92500 Rueil-Malmaison France | RITALINE L.P. | 30mg | modified release capsule | oral |
| FR - France | NOVARTIS PHARMA SAS 2-4 rue Lionel Terray 92500 Rueil-Malmaison France | RITALINE L.P. | 40mg | modified release capsule | oral |
| HU - Hungary | JANSSEN-CILAG Kft. 2045 Törökbálint, Tó Park | CONCERTA 18 mg | 18mg | retard tableta | oral |
| HU - Hungary | JANSSEN-CILAG Kft. 2045 Törökbálint, Tó Park | CONCERTA 36 mg | 36mg | retard tableta | oral |
| HU - Hungary | JANSSEN-CILAG Kft. 2045 Törökbálint, Tó Park | CONCERTA 54 mg | 54mg | retard tableta | oral |
| HU - Hungary | Novartis Hungária Kft.Pharma 1114 Budapest Bartók Béla út 43-47 | RITALIN | 10mg | tablet | oral |
| HU - Hungary | Novartis Hungária Kft.Pharma 1114 Budapest Bartók Béla út 43-47 | RITALIN | 20mg | prolonged release capsules | oral |
| HU - Hungary | Novartis Hungária Kft.Pharma 1114 Budapest Bartók Béla út 43-47 | RITALIN | 30mg | prolonged release capsules | oral |

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| HU - Hungary | Novartis Hungária Kft.Pharma 1114 Budapest Bartók Béla út 43-47 | RITALIN | 40mg | prolonged release capsules | oral |
| IE - Ireland | Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley GU16 7SR, UK | Ritalin | 10mg | Tablet | Oral |
| IE - Ireland | Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley, Camberley GU16 7SR, UK | Ritalin LA | 20mg, 30mg, 40mg | Capsules modified release | Oral |
| IE - Ireland | Janssen-Cilag Ltd, Saunderton, High Wycombe HP14 4HJ, Buckinghamshire, England. | Concerta XL | 18mg, 27mg 36mg, 54mg | Prolonged release tablet | Oral |
| IE - Ireland | Ratiopharm GmbH, Graf-Arco-Strasse 3, D- | Equasym | 5mg, 10mg, 20mg | Tablets | Oral |
| IE - Ireland | Ratiopharm GmbH, Graf-Arco-Strasse 3, D- | Equasym XL | 10mg, 20mg, 30mg | Capsules modified release | Oral |
| IE – Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym 5 mg tablets | 5mg | Tabletss | Oral |
| IE – Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym 10 mg tablets | 10mg | Tablets | Oral |
| IE - Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym 20 mg tablets | 30mg | Tablets | Oral |

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|----------------|--|---|-------|---------------------------------|----------|
| IE - Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym XL 10mg Modified-release capsules, hard | 10 mg | Modified-release capsules, hard | Oral |
| IE - Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym XL 20mg Modified-release capsules, hard | 20 mg | Modified-release capsules, hard | Oral |
| IE - Ireland | UCB (Pharma) Ireland Ltd Magna Drive, Magna Business Park Citywest Road – Dublin 24 Ireland | Equasym XL 30mg Modified-release capsules, hard | 30 mg | Modified-release capsules, hard | Oral |
| LV – Latvia | UAB Johnson & Johnson, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 18 mg | prolonged release tablet | oral use |
| LV – Latvia | UAB Johnson & Johnson, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 36 mg | prolonged release tablet | oral use |
| LV – Latvia | UAB Johnson & Johnson, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 54 mg | prolonged release tablet | oral use |
| LV - Latvia | Novartis Finland Oy, Metsanneidonkuja 10, , FI-02130 Espoo, Finland, | Ritalin 10 mg | 10mg | tablets | oral |
| LT – Lithuania | UAB „Johnson & Johnson“, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 18 mg | prolonged release tablet | oral use |
| LT – Lithuania | UAB „Johnson & Johnson“, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 36 mg | prolonged release tablet | oral use |
| LT – Lithuania | UAB „Johnson & Johnson“, Geležinio Vilko g. 18A, LT-08104 Vilnius, Lithuania. | CONCERTA | 54 mg | prolonged release tablet | oral use |

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| IT- Italy | Janssen- Cilag SpA Via M. Buonarroti 23 20093 Cologno Monzese (MI) - ITALY | CONCERTA | 18 mg 36 mg 54 mg | Prolonged release tablet | oral |
| PT - Portugal | Janssen-Cilag Farmacêutica, Lda. - Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo - 2734-503 Barcarena | Concerta | 18 mg | Prolonged-release tablet | Oral use |
| PT - Portugal | Janssen-Cilag Farmacêutica, Lda. - Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo - 2734-503 Barcarena | Concerta | 27 mg | Prolonged-release tablet | Oral use |
| PT - Portugal | Janssen-Cilag Farmacêutica, Lda. - Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo - 2734-503 Barcarena | Concerta | 36 mg | Prolonged-release tablet | Oral use |
| PT - Portugal | Janssen-Cilag Farmacêutica, Lda. - Estrada Consiglieri Pedroso, 69 A - Queluz de Baixo - 2734-503 Barcarena | Concerta | 54 mg | Prolonged-release tablet | Oral use |
| PT - Portugal | Novartis Farma - Produtos Farmacêuticos, S.A. - Rua do Centro Empresarial - Edifício 8 - Quinta da Beloura - 2710-444 Sintra | Ritalina LA | 20 mg | Modified-release capsule, hard | Oral use |
| PT - Portugal | Novartis Farma - Produtos Farmacêuticos, S.A. - Rua do Centro Empresarial - Edifício 8 - Quinta da Beloura - 2710-444 Sintra | Ritalina LA | 30 mg | Modified-release capsule, hard | Oral use |
| PT - Portugal | Novartis Farma - Produtos Farmacêuticos, S.A. - Rua do Centro Empresarial - Edifício 8 - Quinta da Beloura - 2710-444 Sintra | Ritalina LA | 40 mg | Modified-release capsule, hard | Oral use |
| PT - Portugal | Laboratorios Rubió, S.A. - Calle Industria, 29 - Poligono Industrial | Rubifen | 5 mg | Tablet | Oral use |

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| | Comte de Sert - E-08755 Castellbisbal - Barcelona - Spain | | | | |
| PT - Portugal | Laboratorios Rubió, S.A. - Calle Industria, 29 - Poligono Industrial Comte de Sert - E-08755 Castellbisbal - Barcelona - Spain | Rubifen | 10 mg | Tablet | Oral use |
| PT - Portugal | Laboratorios Rubió, S.A. - Calle Industria, 29 - Poligono Industrial Comte de Sert - E-08755 Castellbisbal - Barcelona - Spain | Rubifen | 20 mg | Tablet | Oral use |
| RO Romania | Janssen-Pharmaceutica N.V. Tumhoutseweg 30 2340 Beerse Belgium | Concerta XL 18 mg | 18 mg | Prolonge release film-coated tablets | |
| RO Romania | Janssen-Pharmaceutica N.V. Tumhoutseweg 30 2340 Beerse Belgium | Concerta XL 36 mg | 36 mg | Prolonge release film-coated tablets | |
| RO Romania | Janssen-Pharmaceutica N.V. Tumhoutseweg 30 2340 Beerse Belgium | Concerta XL 54 mg | 54 mg | Prolonged release film-coated tablets | oral |
| SE – Sweden | Janssen-Cilag AB Box 7073 SE-192 07 Sollentuna Sweden | Concerta | 18, 27 36, 54 mg | prolonged-release tablet | oral |
| SE – Sweden | UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Kobenhavn S Denmark | Equasym Depot | 10, 20, 30 mg | Modified-release capsules, hard | Oral |
| SE – Sweden | Novartis Sverige AB Box 1150 SE-183 11 Täby Sweden | Ritalin | 10, 20, 30, 40 mg | 10 mg – tablet 20, 30, 40 mg – modified- release capsule, hard | oral |

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|------------------------|---|---------------------------|-------------------------|---|----------|
| SE – Sweden | UCB Nordic A/S Arne Jacobsens Allé 15 DK-2300 Kobenhavn S Denmark | Equasym | 5, 10, 20 mg | tablet | oral |
| SE – Sweden | Medice Arzneimittel Pütter & Co. KG Kuhloweg 37-39 DE-58638 Iserlohn Germany | Medikinet | 5, 10, 20, 30, 40 mg | 5, 10, 20 mg – tablet 10, 20, 30, 40 – prolonged- release capsule, hard | oral |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM 10 MG TABLETS | 10MG | TABLET | ORAL USE |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM 5 MG TABLETS | 5MG | TABLET | ORAL USE |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM 20 MG TABLETS | 20MG | TABLET | ORAL USE |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM XL 10 MG CAPSULES | 10MG | MODIFIED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM XL 20 MG CAPSULES | 20MG | MODIFIED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | UCB PHARMA LIMITED, 208 BATH ROAD, SLOUGH, BERKSHIRE SL1 3WE UNITED KINGDOM | EQUASYM XL 30 MG CAPSULES | 30MG | MODIFIED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | NOVARTIS PHARMACEUTICALS UK LIMITED, FRIMLEY BUSINESS PARK, FRIMLEY, CAMBERLEY, SURREY GU16 7SR, UNITED KINGDOM | RITALIN | 10MG | TABLET | ORAL USE |

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| UK – United Kingdom | JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ, UNITED KINGDOM | CONCERTA® XL | 18MG | PROLONGED-RELEASE TABLET | ORAL USE |
| UK – United Kingdom | JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ, UNITED KINGDOM | CONCERTA® XL | 36MG | PROLONGED-RELEASE TABLET | ORAL USE |
| UK – United Kingdom | JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ, UNITED KINGDOM | CONCERTA® XL | 54MG | PROLONGED-RELEASE TABLET | ORAL USE |
| UK – United Kingdom | JANSSEN-CILAG LIMITED, SAUNDERTON, HIGH WYCOMBE, BUCKINGHAMSHIRE, HP14 4HJ, UNITED KINGDOM | CONCERTA® XL | 27MG | PROLONGED-RELEASE TABLET | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET | 5MG | TABLET | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET | 10MG | TABLET | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET | 20MG | TABLET | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET XL | 10MG | PROLONGED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET XL | 20MG | PROLONGED-RELEASE CAPSULE, HARD | ORAL USE |

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| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET XL | 30MG | PROLONGED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | MEDICE ARZNEIMITTEL PUTTER GMBH & CO KG; KUHLOWEG 37; ISERLOHN 58638; GERMANY | MEDIKINET XL | 40MG | PROLONGED-RELEASE CAPSULE, HARD | ORAL USE |
| UK – United Kingdom | ALFRED E TIEFENBACHER GMBH & CO; VAN-DER-SMISSEN-STRASSE 1; HAMBURG D-22767; GERMANY | ELMIFITEN | 10MG | TABLET | ORAL USE |
| UK – United Kingdom | ALFRED E TIEFENBACHER GMBH & CO; VAN-DER-SMISSEN-STRASSE 1; HAMBURG D-22767; GERMANY | TIFINIDAT | 10MG | TABLET | ORAL USE |
| UK – United Kingdom | LABORATORIOS RUBIÓ S A, C/INDUSTRIAL 29, POLIGONO INDUSTRIAL, COMTE DE SERT, CASTELLBISBAL, BARCELONA E-08755, SPAIN | TRANQUILYN | 5MG | TABLET | ORAL USE |
| UK – United Kingdom | LABORATORIOS RUBIÓ S A, C/INDUSTRIAL 29, POLIGONO INDUSTRIAL, COMTE DE SERT, CASTELLBISBAL, BARCELONA E-08755, SPAIN | TRANQUILYN | 10MG | TABLET | ORAL USE |
| UK – United Kingdom | LABORATORIOS RUBIÓ S A, C/INDUSTRIAL 29, POLIGONO INDUSTRIAL, COMTE DE SERT, CASTELLBISBAL, BARCELONA E-08755, SPAIN | TRANQUILYN | 20MG | TABLET | ORAL USE |
| IS Iceland | UCB Nordic A/S c/o Vistor hf. Hörgatúni 2, 212 Garðabær, Iceland | Equasym Depot | 30 mg | Modified-release capsule, hard | Oral |
| IS Iceland | UCB Nordic A/S c/o Vistor hf., Hörgatúni 2, 212 Garðabær, Iceland | Equasym Depot | 20 mg | Modified-release capsule, hard | Oral |

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| IS Iceland | UCB Nordic A/S, c/o Vistor hf., Hörgatúni 2, 212 Garðabær, Iceland | Equasym Depot | 10 mg | Modified-release capsule, hard | Oral |
| IS | Janssen-Cilag AB c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland. | Concerta | 54 mg | Prolonged release tablet | Oral |
| IS | Janssen-Cilag AB c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland. | Concerta | 27 mg | Prolonged release tablet | Oral |
| IS | Janssen-Cilag AB c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland. | Concerta | 36 mg | Prolonged release tablet | Oral |
| IS | Janssen-Cilag AB c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland. | Concerta | 18 mg | Prolonged release tablet | Oral |
| IS Iceland | UCB Nordic A/S, c/o Vistor hf., Hörgatúni 2, 212 Garðabær, Iceland | Equasym | 20 mg | Tablet | Oral |
| IS Iceland | UCB Nordic A/S, c/o Vistor hf., Hörgatúni 2, 212 Garðabær, Iceland | Equasym | 10 mg | Tablet | Oral |
| IS Iceland | UCB Nordic A/S, c/o Vistor hf., Hörgatúni 2, 212 Garðabær, Iceland | Equasym | 5 mg | Tablet | Oral |
| IS | Novartis Healthcare A/S, c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland | Ritalin | 10 mg | Tablet | Oral |
| IS | Novartis Healthcare A/S, c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland | Ritalin Uno | 40 mg | Modified-release capsule, hard | Oral |
| IS | Novartis Healthcare A/S, c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland | Ritalin Uno | 20 mg | Modified-release capsule, hard | Oral |
| IS | Novartis Healthcare A/S, c/o Vistor hf., Hörgatún 2, 212 Garðabær, Iceland | Ritalin Uno | 30 mg | Modified-release capsule, hard | Oral |
| DE – Germany | Novartis Pharma GmbH D-90327 Nuernberg | Ritalin | 10. mg | Tablet | Oral |
| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | MPH Novartis 20 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 20. mg | Modified-release capsule, hard | Oral |
| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | MPH Novartis 30 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 30. mg | Modified-release capsule, hard | Oral |
| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | MPH Novartis 40 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 40. mg | Modified-release capsule, hard | Oral |

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| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | Ritalin LA 20 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 20. mg | Modified-release capsule, hard | Oral |
| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | Ritalin LA 30 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 30. mg | Modified-release capsule, hard | Oral |
| DE - Germany | Novartis Pharma GmbH D-90327 Nuernberg | Ritalin LA 40 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 40. mg | Modified-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet 10mg | 11.56 mg | Tablet | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym 5 mg Tabletten | 5. mg | Tablet | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym 20 mg Tabletten | 20. mg | Tablet | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid 10mg | 11.56 mg | Tablet | Oral |
| DE - Germany | Alfred E.Tiefenbacher GmbH & Co.KG Van-der-Smissen-Str. 1 D-22767 Hamburg | Methylphenidat TB | 11.56 mg | Tablet | Oral |
| DE - Germany | HEXAL AG Postfach 1263 D-83602 Holzkirchen | Methylphenidat HEXAL 10mg Tabletten | 10 mg | Tablet | Oral |

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| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet 5 mg | 5. mg | Tablet | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet 20 mg | 20. mg | Tablet | Oral |
| DE - Germany | Janssen-Cilag GmbH 41457 Neuss or Janssen Cilag GmbH Raiffeisenstr.8 41470 Neuss, Germany | CONCERTA 18 mg Retardtabletten | 18. mg | Prolonged-release tablet | Oral |
| DE - Germany | Janssen-Cilag GmbH 41457 Neuss or Janssen Cilag GmbH Raiffeisenstr.8 41470 Neuss, Germany | CONCERTA 27 mg Retardtabletten | 27. mg | Prolonged-release tablet | Oral |
| DE - Germany | Janssen-Cilag GmbH 41457 Neuss or Janssen Cilag GmbH Raiffeisenstr.8 41470 Neuss, Germany | CONCERTA 36 mg Retardtabletten | 36. mg | Prolonged-release tablet | Oral |
| DE - Germany | Janssen-Cilag GmbH 41457 Neuss or Janssen Cilag GmbH Raiffeisenstr.8 41470 Neuss, Germany | CONCERTA 54 mg Retardtabletten | 54. mg | Prolonged-release tablet | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet retard 10 mg | 10. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet retard 20 mg | 20. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet retard 5 mg | 5. mg | Prolonged-release capsule, hard | Oral |

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| DE - Germany | TAD Pharma GmbH Postfach 720 D-27457 Cuxhaven | METHYLPHENI TAD 5 mg Tabletten | 5. mg | Tablet | Oral |
| DE - Germany | TAD Pharma GmbH Postfach 720 D-27457 Cuxhaven | METHYLPHENI TAD 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | TAD Pharma GmbH Postfach 720 D-27457 Cuxhaven | METHYLPHENI TAD 20 mg Tabletten | 20. mg | Tablet | Oral |
| DE - Germany | ratiopharm GmbH D-89070 Ulm | Methylphenidat-ratiopharm 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | Alfred E.Tiefenbacher GmbH & Co.KG Van-der-Smissen-Str. 1 D-22767 Hamburg | Elmifiten 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | 1 A Pharma GmbH Keltenring 1 + 3 D-82041 Oberhaching | Methylphenidat - 1 A Pharma 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | Alfred E.Tiefenbacher GmbH & Co.KG Van-der-Smissen-Str. 1 D-22767 Hamburg | Tifinidat 10 mg Tabletten | 10. mg | Tablet | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet retard 30 mg | 30. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikinet retard 40 mg | 40. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid 5 mg | 5. mg | Tablet | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid 20 mg | 20. mg | Tablet | Oral |

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| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid retard 10 mg | 10. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid retard 20 mg | 20. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid retard 5 mg | 5. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym retard 10 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 10 mg | Modified-release capsule, hard | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym retard 20 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 20. mg | Modified-release capsule, hard | Oral |
| DE - Germany | UCB GmbH Alfred-Nobel-Str. 10 D-40789 Monheim Germany | Equasym retard 30 mg Hartkapseln mit veränderter Wirkstofffreisetzung | 30 mg | Modified-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid retard 30 mg | 30. mg | Prolonged-release capsule, hard | Oral |
| DE - Germany | Medice Postfach 2063 D-58634 Iserlohn | Medikid retard 40 mg | 40. mg | Prolonged-release capsule, hard | Oral |
| EL - Greece | JANSSEN-CILAG PHARMACEUTICAL S.A.C.I EIRINIS AVENUE 56, PEFKI, 15121 Tel: +30-210-6140061 Fax: +30-210-6140072 | CONCERTA® | 18 MG 36 MG 54 MG | PROLONGED RELEASE TABLETS | ORAL |

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| EL - Greece | LABORATORIOS RUBIO S.A. C/Industria 29 Pol. Compte de Sert 08755-Castellbisbal (Barcelona) SPAIN Tel: +34-93-772 25 09 Fax: +34-93-772 25 01 | METHYLPHENIDATE/RUBIO | 5 MG/TAB 10 MG/TAB 20 MG/TAB | TABLETS | ORAL |
| EL - Greece | UCB A.E. VOULIAGMENIS AVENUE 580, ARGYROUPOLIS 16452 | EQUASYM XR | 10, 20, 30 mg | Modified-release capsules, hard | ORAL |
| IT | NOVARTIS FARMA S.P.A. Largo Umberto Boccioni 1 21040 VARESE | RITALIN | 10 mg | Tablet 30 | Oral |
| IT | NOVARTIS FARMA S.P.A. Largo Umberto Boccioni 1 21040 VARESE | RITALIN | 20 mg | Tablet prolonged release 30 | Oral |
| IT | NOVARTIS FARMA S.P.A. Largo Umberto Boccioni 1 21040 VARESE | RITALIN | 20 mg | Tablet prolonged release 100 | Oral |
| MT - Malta | Novartis Pharmaceuticals UK Ltd, Frimley Business Park, Frimley Camberley, Surrey GU16 7SR United Kingdom | Ritalin | 10mg | tablet | oral |
| MT - Malta | UCB Pharma Limited, 208, Bath Road, Slough, Berkshire SL1 3WE United Kingdom | Equasym XL | 10 mg | Modified release capsule, hard. | oral |
| MT - Malta | UCB Pharma Limited, 208, Bath Road, Slough, Berkshire SL1 3WE United Kingdom | Equasym XL | 20 mg | Modified release capsule, hard. | oral |
| MT - Malta | UCB Pharma Limited, 208, Bath Road, Slough, Berkshire SL1 3WE United Kingdom | Equasym XL | 30 mg | Modified release capsule, hard. | Oral |

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| MT - Malta | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 18 mg | prolonged-release tablet | oral use |
| MT - Malta | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 36 mg | prolonged-release tablet | oral use |
| MT - Malta | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 54 mg | prolonged-release tablet | oral use |
| NL - Netherlands | Novartis Pharma B.V.; Raapopseweg 1; 6824 DP ARNHEM/NL | Ritalin | 10 mg | tablets | oral |
| NL - Netherlands | Ratiopharm Nederland BV; Ronde Tocht 11;1507 CC ZAANDAM/NL | Methylfenidaat HCl ratiopharm 10 mg | 10 mg | tablets | oral |
| NL - Netherlands | U.C.B. Pharma B.V.; Lage Mosten 33 ; 4822 NK BREDA/NL | Equasym 5 mg Tabletten | 5 mg | tablets | oral |
| NL - Netherlands | U.C.B. Pharma B.V.; Lage Mosten 33 ; 4822 NK BREDA/NL | Equasym 10 mg tabletten | 10 mg | tablets | oral |
| NL - Netherlands | U.C.B. Pharma B.V.; Lage Mosten 33 ; 4822 NK BREDA/NL | Equasym XL 10 mg Capsule | 10 mg | modified release capsules | oral |
| NL - Netherlands | U.C.B. Pharma B.V.; Lage Mosten 33 ; 4822 NK BREDA/NL | Equasym XL 20 mg Capsule | 20 mg | modified release capsules | oral |
| NL - Netherlands | U.C.B. Pharma B.V.; Lage Mosten 33 ; 4822 NK BREDA/NL | Equasym XL 30 mg Capsule | 30 mg | modified release capsules | oral |
| NL - Netherlands | Alfred Tiefenbacher (GmbH & Co. KG); Van-der-Smisse- Strasse 1; 22767 HAMBURG/ Germany | Methylfenidaat HCl AET 10 mg | 10 mg | tablets | oral |
| NL - Netherlands | Pharmachemie B.V.; Swensweg 5; 2003 RN HAARLEM/NL | Methylfenidaat HCl 10 mg PCH | 10 mg | tablets | oral |
| NL - Netherlands | Hexal B.V.; Pastoorlaan 28; 2182 BX HILLEGOM/NL | Methylfenidaat HCl 10 mg tabletten | 10 mg | tablets | oral |

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| NL - Netherlands | Alfred Tiefenbacher (GmbH & Co. KG); Van-der-Smisse- Strasse 1; 22767 HAMBURG/ Germany | Tifinidat | 10 mg | tablets | oral |
| NL - Netherlands | Janssen-Cilag B.V.; Dr. Paul Janssenweg 150 ; 5026 RH TILBURG/NL | Concerta 18 mg | 18 mg | prolonged release tablets | oral |
| NL - Netherlands | Janssen-Cilag B.V.; Dr. Paul Janssenweg 150 ; 5026 RH TILBURG/NL | Concerta 27 mg | 27 mg | prolonged release tablets | oral |
| NL - Netherlands | Janssen-Cilag B.V.; Dr. Paul Janssenweg 150 ; 5026 RH TILBURG/NL | Concerta 36 mg | 36 mg | prolonged release tablets | oral |
| NL - Netherlands | Janssen-Cilag B.V.; Dr. Paul Janssenweg 150 ; 5026 RH TILBURG/NL | Concerta 54 mg | 54 mg | prolonged release tablets | oral |
| NL - Netherlands | Laboratorios Rubio, S.A.; C\Industria, no. 29 Pol. Ind. Comte de Sert; 08755 CASTELLBISBAL, BARCELONA/ SPAIN | Methylfenidaat HCl 5 mg | 5 mg | tablets | oral |
| NL - Netherlands | Laboratorios Rubio, S.A.; C\Industria, no. 29 Pol. Ind. Comte de Sert; 08755 CASTELLBISBAL, BARCELONA/ SPAIN | Methylfenidaat HCl 10 mg | 10 mg | tablets | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet 5 mg | 5 mg | tablets | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet 10 mg | 10 mg | tablets | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet 20 mg | 20 mg | tablets | oral |

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| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet CR 10 mg | 10 mg | modified release capsules | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet CR 20 mg | 20 mg | modified release capsules | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet CR 30 mg | 30 mg | modified release capsules | oral |
| NL - Netherlands | Medice Arzneimittel Pütter GmbH; Kuhloweg 37; 58638 ISERLOHN/Germany | Medikinet CR 40 mg | 40 mg | modified release capsules | oral |
| NO Norway | Janssen-Cilag AS Hoffsveien 1D 0275 Oslo, Norway | Concerta | 18mg 36 mg 54 mg | prolonged-release tablet | oral |
| NO Norway | UCB Nordic A/S Arne Jacobsens Allé 15 2300 København S Denmark | Equasym tableter 5 mg | 5 mg | tablet | oral |
| NO Norway | UCB Nordic A/S Arne Jacobsens Allé 15 2300 København S Denmark | Equasym tableter 10 mg | 10 mg | tablet | oral |
| NO - Norway | UCB Nordic A/S Arne Jacobsens Allé 15 2300 København S Denmark | Equasym tableter 20 mg | 20 mg | tablet | oral |
| NO | UCB Nordic A/S Arne Jacobsens Allé 15 2300 København S Denmark | Equasym Depot | 10 mg 20 mg 30 mg | modified-release capsule, hard | oral |

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| NO | Novartis Norge AS Brynsalleen 4 0667 Oslo, Norway | Ritalin | 10 mg 20 mg 30 mg 40 mg | (10 mg - tablet) (20 mg, 30 mg, 40 mg - modified-release capsule, hard) | oral |
| NO | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 58638 Iserlohn Nordrhein-Westfalen, Germany | Medikinet | 10 mg 20 mg 30 mg 40 mg | prolonged-release tablet | oral |
| NO | Medice Arzneimittel Pütter GmbH & Co KG Kuhloweg 37 58638 Iserlohn Nordrhein-Westfalen, Germany | Medikinet | 5 mg 10 mg 20 mg | tablet | oral |
| PL - Poland | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 18 mg | prolonged-release tablet | oral use |
| PL - Poland | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 36 mg | prolonged-release tablet | oral use |
| PL - Poland | Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse Belgium | Concerta® | 54 mg | prolonged-release tablet | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet 5 mg | 5 mg | tablet | oral use |

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| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet 10 mg | 10 mg | tablet | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet 20 mg | 20 mg | tablet | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet CR 10 mg | 10 mg | prolonged-release capsule | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet CR 20 mg | 20 mg | prolonged-release capsule | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet CR 30 mg | 30 mg | prolonged-release capsule | oral use |
| PL - Poland | Medice Arzneimittel Pütter GmbH & Co. KG Kuhloweg 37 58638 Iserlohn Germany | Medikinet CR 40 mg | 40 mg | prolonged-release capsule | oral use |

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| LU | Novartis Pharma Roonstrasse 25 90429 Nürnberg Germany | Ritalin | 10 mg | Tablets | Oral |
| LU Luxembourg | Janssen Cilag N.V./S.A Roderveldlaan 1, B- 2600 Berchem | Concerta | 18 mg | Prolonged release tablets | Oral use |
| LU Luxembourg | Janssen Cilag N.V./S.A Roderveldlaan 1, B- 2600 Berchem | Concerta | 27 mg | Prolonged release tablets | Oral use |
| LU Luxembourg | Janssen Cilag N.V./S.A Roderveldlaan 1, B- 2600 Berchem | Concerta | 36 mg | Prolonged release tablets | Oral use |
| LU Luxembourg | Janssen Cilag N.V./S.A Roderveldlaan 1, B- 2600 Berchem | Concerta | 54 mg | Prolonged release tablets | Oral use |
| LU | Medice Arzneimittel Pütter GmbH & Co Kuhloweg 37 58638 Iserlohn Germany | Medikinet | 5 mg | tablets | oral |
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet | 10 mg | tablets | oral |
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet | 20 mg | Tablets | oral |
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet retard | 10 mg | Capsules | Oral |
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet retard | 20 mg | Capsules | Oral |

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|---------------|--|---|-------|---------------------------|----------|
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet retard | 30 mg | Capsules | Oral |
| LU | Medice Arzneimittel Pütter GmbH & Co | Medikinet retard | 40 MG | Capsules | Oral |
| SI | Johnson & Johnson d.o.o. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta 18 mg tablete s podaljšanim sproščanjem | 18 mg | Prolonged release tablets | Oral use |
| SI | Johnson & Johnson d.o.o. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta 36 mg tablete s podaljšanim sproščanjem | 36 mg | Prolonged release tablets | Oral use |
| SI | Johnson & Johnson d.o.o. Smartinska 53, 1000 Ljubljana, Slovenia | Concerta 54 mg tablete s podaljšanim sproščanjem | 54 mg | Prolonged release tablets | Oral use |
| SK – Slovakia | Johnson & Johnson, s. r. o. Plynárenská 7/B 824 78 Bratislava Slovak republic | Concerta 18 mg tablety s predĺženým uvoľňovaním | 18 mg | Prolonged-release tablet | oral use |
| SK – Slovakia | Johnson & Johnson, s. r. o. Plynárenská 7/B 824 78 Bratislava Slovak republic | Concerta 36 mg tablety s predĺženým uvoľňovaním | 36 mg | Prolonged-release tablet | oral use |
| SK – Slovakia | Johnson & Johnson, s. r. o. Plynárenská 7/B 824 78 Bratislava Slovak republic | Concerta 54 mg tablety s predĺženým uvoľňovaním | 54 mg | Prolonged-release tablet | oral use |

ANNEX II

**SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY
OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE
EMA**

SCIENTIFIC CONCLUSIONS

1. Introduction

On 22 June 2007, the European Commission requested a referral to the CHMP under Article 31 of Directive 2001/83/EC, as amended, for all methylphenidate containing products. The EC considered that some safety concerns, including cardiovascular and cerebrovascular disorders, potentially associated with methylphenidate treatment should be evaluated.

Methylphenidate has been available in Europe for decades for the treatment of attention deficit hyperactivity disorder (ADHD) in children aged 6 years and older. It is an amphetamine-like drug that has controlled drug status, which imposes restrictions on prescribing and handling.

Methylphenidate is indicated as a part of a comprehensive treatment programme for ADHD in children over 6 years of age where remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Drug treatment is usually discontinued during or after puberty.

ADHD is defined by 'core' signs of lack of attention, hyperactivity and impulsiveness. ADHD often occurs along with other (co-morbid) disorders such as oppositional defiant and conduct disorders, learning disorders, anxiety, depression, tic disorders and Tourette's syndrome. Though the diagnostic criteria for ADHD exclude children with developmental disorders, such as Asperger Syndrome, some clinicians argue that these conditions can coexist.

Children with severe ADHD can develop poor self-esteem, emotional and social problems. ADHD can also have a severe effect on a child's education. For some of these children, methylphenidate treatment, along with other forms of non-medical treatment can reduce symptoms of hyperactivity and improve quality of life. The signs of ADHD may persist into adolescence and adulthood, and may be associated with continuing emotional and social problems, unemployment, criminality and substance misuse.

2. Safety overview

The regulatory status of the different Methylphenidate containing medicinal products is heterogeneous across EU Member States (MS). Heterogeneity exists in both the availability of the different products across MS and among the product information between products.

The safety evaluation of this procedure is mainly focussed on the following concerns potentially associated with methylphenidate treatment: cardiovascular risks, cerebrovascular risks, psychiatric disorders, carcinogenicity, effect on growth and effects of long term treatment. These concerns are individually discussed in the following sections.

The product information (PI) of most products contains key elements on the above safety concerns of methylphenidate. However, a harmonisation exercise between products is deemed one of the main scopes of this procedure to ensure the same level of health protection in all Member States where methylphenidate products are authorised.

2.1 Cardiovascular risk

2.1.a Data from clinical trials

Overall, the data relating to cardiovascular risks from all clinical trials of methylphenidate-containing products showed that the events of hypertension, heart rate increases or arrhythmias (mainly tachycardia) and QT prolongation were the main cardiovascular events reported. The analysis of the data provided by MAHs showed a highly variable effect of methylphenidate on blood pressure and

heart rate. Where analyses of medical history or concurrent medications were provided, these did not provide conclusive evidence of predictive risk factors for cardiovascular effects of methylphenidate. Methylphenidate has a well-documented effect on blood pressure and heart rate (increased pulse rate, increased blood pressure and tachycardia are recognised adverse events of methylphenidate and are listed in the product information).

Although the data provided suggested that in most patients, these effects are reversible upon discontinuation, there is a lack of reliable data regarding the extent of the effect of methylphenidate on blood pressure and heart rate and also on the long-term effects or clinical consequences on the cardiovascular system of these effects.

2.1.b Data from spontaneous reports

During the procedure the MAHs have been requested to submit data from spontaneous reports. The data submitted on the risk of cardiovascular disorders covered a range of reporting periods. Although most reports occurred in children and adolescents, there was a higher than expected number of reports in adults (where age was reported) for all of the key adverse event terms.

Overall, cardiovascular events reported were mainly of cardiac arrhythmias (including tachycardia), hypertension, cardiac arrests, ischemia, QT prolongation, with some reports of sudden death. Where indication was reported, this was most commonly ADHD, but there were also a significant proportion of reports with other indications reported.

There was no consistent pattern of dosage or time-to-onset from the submitted data.

A clear safety signal for Reynaud's phenomenon was detected and the CHMP's opinion is that there is sufficient evidence from the reviewed data to suspect a causal relationship between methylphenidate use and these reactions. All MAHs are therefore required to add Reynaud's phenomenon to their Product Information (PI) for all methylphenidate-containing products.

2.1.c Pre-clinical data

The pre-clinical data on the risk of cardiovascular disorders submitted suggested that methylphenidate does not have an effect on rapidly activating inward rectifying potassium channels (which play a role in neuronal excitability and heart rate) or on action potential duration. However, a sympathomimetic effect on the cardiovascular system was considered plausible. Additionally, there was some pre-clinical evidence of a direct effect of methylphenidate on the structure of cardiac tissue. The reviews of the published literature and epidemiological data reached the same conclusion.

2.1.d Cyanosis

There was no evidence from pre-clinical or clinical trial data of an increased risk of cyanosis with methylphenidate. Post-marketing reports included cases of central, peripheral and unspecified cyanosis. The product information for most of the methylphenidate-containing products in the EU contain warnings for use in patients with underlying cardiac disorders and lists many of the disorders reported with cyanosis as possible ADRs in section 4.8. Peripheral coldness and Reynaud's phenomenon are also listed as possible reactions in section 4.8 of some of the SPCs for methylphenidate. MAHs are requested to list these terms in the PI for those products where the information is missing. The MAHs should closely monitor reports of cyanosis in future PSURs, including them as terms for targeted follow-up.

In conclusion regarding the cardiovascular risks, it is accepted that there is a potential risk. For that reason the CHMP requested strengthening of the Product Information giving advice on pre-treatment evaluation of the patients and on going screening and monitoring during the treatment with these products (see Annex III). In addition the CHMP also requested that a consistent and structured approach is taken in the future for the assessment of the safety information in the Period Safety Assessment Reports (PSURs) and the Risk Management Plans. Furthermore, the results of the ongoing

studies focusing on this issue, once available, will be submitted for assessment as requested by the CHMP (see Annex IV).

2.2 Cerebrovascular risk

There was no evidence reported from pre-clinical studies in relation to this risk.

Most cerebrovascular events from clinical trials were of migraine, with a higher incidence rate in methylphenidate-treated group compared with placebo group. No events related to other cerebrovascular disorders were reported in children from clinical trials.

The MAH review of post-marketing spontaneous data found that cerebrovascular events from spontaneous reports consisted mainly of the reported terms: cerebrovascular accident, stroke, cerebral infarction and cerebral ischemia as well as a few reports of other events. There were un-confounded cases with no underlying history of cerebrovascular disorders, reporting cerebral infarction and cerebral artery occlusion; right cerebral occlusion and cerebral ischaemic event. The submitted data suggested that events occurred within the recommended doses.

Finally as requested by the CHMP the relevant sections of the Product Information are amended to harmonise the safety information on the cerebrovascular risk. The CHMP also requested that a consistent and structured approach is taken in the future for the assessment of the safety information in the Period Safety Assessment Reports (PSURs) and the Risk Management Plans. In addition the results of the ongoing studies focusing on this issue, once available, will be submitted for assessment as requested by the CHMP (see Annex IV).

2.3 Psychiatric risk

Psychiatric adverse events of particular interest with methylphenidate reported from clinical trials included aggression, violent behaviour, psychosis, mania, irritability and suicidality. Where provided, the information on drug dechallenge suggested that methylphenidate may play a causative role in the development of serious psychiatric disorders.

Most frequently reported psychiatric adverse events of interest from spontaneous reports were abnormal behaviour, abnormal thinking, anger, hostility, aggression, agitation, tic, irritability, anxiety, crying, depression, somnolence, aggravated ADHD, psychomotor hyperactivity, emotional disorder, anger, nervousness, psychotic disorder, mood swings, morbid thoughts, obsessive-compulsive disorder, personality change/disorder, restlessness, confusional state, hallucinations, lethargy, paranoia and suicidality.

Review of the pre-clinical data in the responses shows that methylphenidate causes behavioural changes in animal models, mainly as hyperactivity and stereotyped behaviour.

The literature also suggests that methylphenidate can exacerbate psychiatric disorders in patients with ADHD. The difficulty in determining the effects of methylphenidate in most of the studies due to the co-morbidity between ADHD and psychiatric disorders was also noted.

A review of all available data found that the more specific terms “over-focussing” and “repetitive behaviours” reflect the observed effects of methylphenidate and should be added as possible adverse effects in the Product Information. In addition the results of the ongoing study on suicidality will be submitted once available and the MAHs undertook the commitment to investigate psychiatric outcomes in a future long-term study.

2.4 Effects on Growth

There was some evidence from pre-clinical studies showing an effect of methylphenidate on some growth parameters, sexual maturation and related hormones as well as on developmental toxicity. However, these findings were not consistent across all the reviewed studies.

The completed clinical studies presented a range of conclusions on the effects of methylphenidate on growth and sexual maturation. The literature is conflicting with regards to the effects of methylphenidate on growth and sexual maturation. The ongoing Studies on growth, and on sexual maturation should provide valid data on those possible risks.

Overall, it can be concluded that the exact causal mechanism for the effects of methylphenidate on growth remains uncertain. The PI for all methylphenidate-containing products have warnings related to this point in section 4.4 of the SPC. The text differed among MAHs, but the recommendation of baseline assessment and monitoring of growth was common to most products.

The CHMP therefore agreed that in order to ensure any effect on growth is minimised, improved and harmonised warnings, guidelines on monitoring (frequency of monitoring, method of measurement) and actions to take, should be implemented in the SPC and the PL. In addition the CHMP requested that new studies on long-term effects on development are carried out. The MAHs have committed to it.

2.5 Leukaemia

Recent findings from a case-control study have indicated a potentially increased risk of lymphocytic leukaemia with methylphenidate, which the MAHs were required to further evaluate. The MAHs submitted data supporting the position that there is no preclinical or clinical evidence for a significant carcinogenic risk associated with methylphenidate. Methylphenidate may have some activity as a non-genotoxic carcinogen in mouse liver; however, the limited human analyses do not suggest that this activity is reproduced in humans exposed to therapeutic doses.

The recently published retrospective case control review of prescription records for more than 35,000 patients did not indicate either a moderate or a strong association between methylphenidate use and cancer risk in children for any of 18 defined cancer sites. This only study raises a potential signal of risk of leukaemia with methylphenidate use, despite the limitations of the findings, as discussed by the authors and the MAHs. A currently ongoing cytogenicity study may give responses when finalised. The MAHs will submit the results for assessment when available. The CHMP concluded that the current initiatives to further evaluate any risk of carcinogenicity with methylphenidate are endorsed.

2.6 Effects of long term treatment

Some pre-clinical evidence was submitted suggesting that there is a differential effect of acute vs. chronic treatment with methylphenidate on expression of genes involved in neuronal plasticity, a differential effect of methylphenidate exposure in juveniles vs adults on expression of central neurotransmitter receptors and an effect of treatment in adolescence on survival of new brain cells.

Aside from the issue of growth, there is lack of adequate clinical or pharmacoepidemiological data on the effects of long-term treatment with methylphenidate in the EU, in relation to cardiovascular, cerebrovascular, psychiatric, carcinogenicity or any other long-term risks.

It is widely accepted (from review of the literature) that long-term safety and effectiveness of methylphenidate has not been conclusively proven in suitably designed and conducted studies.

The MAHs undertook the commitment to investigate the feasibility of a long term study on the children development and to provide a study protocol, as requested by the CHMP.

2.7 Off-label use/misuse/diversion

The significant risks of off-label use, misuse and diversion were identified from the submitted data. Cumulative reviews showed that a large proportion of post-marketing cases analysed were used in indications not related to ADHD. Some of these were conditions in which the use of methylphenidate is warned against or contra-indicated.

Methylphenidate is not indicated for use in patients who may display some symptoms of ADHD but have not been formally diagnosed. Therefore strengthening the Product Information and giving guidance to prescribers on the correct use is necessary. The MAHs have committed to distribute education material for guidance of the prescribers. In addition the MAHs have committed to perform drug utilisation studies (DUS) in all EU MS to investigate the level of misuse, as requested by the CHMP.

2.8 Pregnancy and lactation

The safety of the use of methylphenidate containing products during pregnancy and lactation has been assessed by the CHMP and further discussed in the Safety Working Party (SWP) in December 2008. In general there are no signs of teratogenicity in animals. The SPC has been amended accordingly.

3. Overall Safety Discussion and Conclusion

This scientific assessment on methylphenidate has reviewed the available safety data from clinical trials, preclinical studies, spontaneous reports and published literature.

The main objective was the cardiovascular risk of the product to children but additionally other risks were also evaluated; cerebrovascular, effect on growth and long term treatment, the psychiatric risk and a potential risk of leukaemia.

Following the discussions at the CHMP it was agreed that long-term use data is still needed on a potential effect of methylphenidate on cardiovascular and cerebrovascular events. In addition more data is needed to assess the psychiatric outcome as well as the effect on growth and development of the children. So, there is the need for this information to be clear to the prescribers and the public by strengthening the wording of the Product Information of the products. In addition, clinical studies investigating the issues are currently ongoing and the final reports will be submitted to the regulatory authorities. Furthermore, the MAHs committed to investigate the long term effect on children's development. On going studies on sex maturation will also provide new data in this aspect.

In terms of the suicidality the MAHs committed to make use of the current knowledge and to conduct a meta-analysis on the available results from different clinical studies.

In addition risk minimisation measures need to be in place in order to continuously identify and evaluate potential risks. The MAHs committed to it.

The conclusions of this assessment led to a CHMP proposal on strengthening and harmonising the respective Product Information of the products with the inclusion of pre- and post-treatment monitoring, updating the sections of the SPC related to the contraindications and warnings, harmonising the information on adverse reactions, checking of the posology and use, updating the information on use in pregnancy and lactation.

The update proposed for the SPC was reflected into the PL. The PL will be tested for User readability and the results will be submitted to the regulatory Authorities.

In addition the harmonisation of the submission of the PSURs and the Risk Management Plans (RMP) by the MAHs will insure that the safety information is assessed simultaneously by the Members States via the PhVWP and the continuity of the harmonisation will be ensured.

4. Benefit/risk

Taking all these elements into account, the CHMP concluded that the benefit/risk ratio for methylphenidate containing products in the treatment of ADHD in children aged six and above, is considered favourable and recommended the maintenance of the Marketing Authorisation in accordance to the amendments of the Summary of Product Characteristics, and Package Leaflet (set out in Annex III) for the medicinal products referred to in Annex I.

GROUNDINGS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing methylphenidate initiated by the European Commission.
- The Committee considered all the available data submitted on the safety of the methylphenidate containing products.
- The Committee, considered the benefit/risk balance of medicinal products containing methylphenidate in the treatment of ADHD in children aged 6 years and over and in adolescents in the EU. This included assessment on the impact of risks of cardiovascular, cerebrovascular and psychiatric disorders on the benefit/risk balance. The risk of carcinogenicity, effects on growth and the effects of long-term treatment were also evaluated.
- The CHMP concluded that the Product Information of all methylphenidate-containing products should include the same safety information and therefore recommended the harmonisation of relevant sections of the Summaries of Product Characteristics and Package Leaflets. Furthermore, the Risk Management Plans of these products should also be harmonised.

As a consequence, the CHMP has recommended the maintenance of the Marketing Authorisations for the medicinal products referred to in Annex I for which the amendments to the relevant sections of the Summary of Product Characteristics and Package Leaflet are set out in Annex III

ANNEX III

**AMENDMENTS TO THE SUMMARY OF PRODUCT CHARACTERISTICS AND
PACKAGE LEAFLET**

SUMMARY OF PRODUCT CHARACTERISTICS

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

...[]...

Attention-Deficit/Hyperactivity Disorder (ADHD)

Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit / hyperactivity disorder (ADHD) in children aged 6 years of age and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. Diagnosis cannot be made solely on the presence of one or more symptom.

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a stimulant must be based on rigorous assessment of the severity of the child's symptoms. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

4.2 Posology and method of administration

...[]...

Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.

Pre-treatment screening:

Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present co-morbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death and accurate recording of pre-treatment height and weight on a growth chart (see sections 4.3 and 4.4)

Ongoing monitoring:

Growth, psychiatric and cardiovascular status should be continuously monitored (see also Section 4.4).

- Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months;

- height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart;
- development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate.

Dose titration

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

Other strengths of this medicinal product and other methylphenidate-containing products may be available.

{The MA Holder should describe the dose conversion (between formulations) and the dose titration steps that are relevant to the formulation and strength of their own methylphenidate product, in each methylphenidate SPC in the EU}

The maximum daily dosage of methylphenidate is *{to be completed nationally}*.

Long-term (more than 12 months) use in children and adolescents

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to assess the child's condition (preferable during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Dose reduction and discontinuation

Treatment must be stopped if the symptoms do not improve after appropriate dosage adjustment over a one-month period. If paradoxical aggravation of symptoms or other serious adverse events occur, the dosage should be reduced or discontinued.

Adults

Methylphenidate is not licensed for use in adults in ADHD. Safety and efficacy have not been established in this age group

Elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Children under 6 years of age

Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

4.3 Contraindications

...[]...

Known sensitivity to methylphenidate or any of the excipients

- Glaucoma
- Pheochromocytoma
- During treatment with non-selective, irreversible monoamine oxidase (MAO) inhibitors, or within a minimum of 14 days of discontinuing those drugs, due to risk of hypertensive crisis (see section 4.5)
- Hyperthyroidism or Thyrotoxicosis
- Diagnosis or history of severe depression, anorexia nervosa/anorexic disorders, suicidal tendencies, psychotic symptoms, severe mood disorders, mania, schizophrenia, psychopathic/borderline personality disorder.
- Diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder (that is not well-controlled)
- pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).
- pre-existing cerebrovascular disorders cerebral aneurysm, vascular abnormalities including vasculitis or stroke

4.4 Special warnings and precautions for use

...[]...

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age.

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long term use of methylphenidate has not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not, be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring according to the guidance in sections 4.2 and 4.4. for cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric disorders. Psychiatric disorders to monitor for are described below, and include (but are not limited to) motor or vocal tics, aggressive or hostile behaviour, agitation, anxiety, depression, psychosis, mania, delusions, irritability, lack of spontaneity, withdrawal and excessive perseveration.

The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is de-challenged at least once yearly to

assess the child's condition (preferably during times of school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued.

Use in adults

Methylphenidate is not licensed for use in adults with ADHD. Safety and efficacy have not been established in this age group

Use in the elderly

Methylphenidate should not be used in the elderly. Safety and efficacy has not been established in this age group.

Use in children under 6 years of age

Methylphenidate should not be used in children under the age of 6 years. Safety and efficacy in this age group has not been established.

Cardiovascular status

Patients who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden cardiac or unexplained death or malignant arrhythmia,) and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease. Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during methylphenidate treatment should undergo a prompt specialist cardiac evaluation.

Analyses of data from clinical trials of methylphenidate in children and adolescents with ADHD showed that patients using methylphenidate may commonly experience changes in diastolic and systolic blood pressure of over 10 mmHg relative to controls. The short- and long-term clinical consequences of these cardiovascular effects in children and adolescents are not known, but the possibility of clinical complications cannot be excluded as a result of the effects observed in the clinical trial data. **Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate.** See section 4.3 for conditions in which methylphenidate treatment is contraindicated.

Cardiovascular status should be carefully monitored. Blood pressure and pulse should be recorded on a centile chart at each adjustment of dose and then at least every 6 months.

The use of methylphenidate is contraindicated in certain pre-existing cardiovascular disorders **unless specialist paediatric cardiac advice has been obtained (see Section 4.3 'Contraindications')**.

Sudden death and pre-existing cardiac structural abnormalities or other serious cardiac disorders

Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children, some of whom had cardiac structural abnormalities or other serious heart problems. Although some serious heart problems alone may carry an increased risk of sudden death, stimulant products are not recommended in children or adolescents with known cardiac structural abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant medicine.

Misuse and Cardiovascular Events

Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.

Cerebrovascular disorders

See section 4.3 for cerebrovascular conditions in which methylphenidate treatment is contraindicated. Patients with additional risk factors (such as a history of cardiovascular disease, concomitant

medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with methylphenidate.

Cerebral vasculitis appears to be a very rare idiosyncratic reaction to methylphenidate exposure. There is little evidence to suggest that patients at higher risk can be identified and the initial onset of symptoms may be the first indication of an underlying clinical problem. Early diagnosis, based on a high index of suspicion, may allow the prompt withdrawal of methylphenidate and early treatment. The diagnosis should therefore be considered in any patient who develops new neurological symptoms that are consistent with cerebral ischemia during methylphenidate therapy. These symptoms could include severe headache, numbness, weakness, paralysis, and impairment of coordination, vision, speech, language or memory..

Treatment with methylphenidate is not contraindicated in patients with hemiplegic cerebral palsy

Psychiatric disorders

Co-morbidity of psychiatric disorders in ADHD is common and should be taken into account when prescribing stimulant products. In the case of emergent psychiatric symptoms or exacerbation of pre-existing psychiatric disorders, methylphenidate should not be given unless the benefits outweigh the risks to the patient.

Development or worsening of psychiatric disorders should be monitored at every adjustment of dose, then at least every 6 months, and at every visit; discontinuation of treatment may be appropriate.

Exacerbation of pre-existing Psychotic or manic symptoms

In psychotic patients, administration of methylphenidate may exacerbate symptoms of behavioural disturbance and thought disorder.

Emergence of new psychotic or manic symptoms

Treatment-emergent psychotic symptoms (visual/tactile/auditory hallucinations and delusions) or mania in children and adolescents without prior history of psychotic illness or mania can be caused by methylphenidate at usual doses. If manic or psychotic symptoms occur, consideration should be given to a possible causal role for methylphenidate, and discontinuation of treatment may be appropriate.

Aggressive or hostile behaviour

The emergence or worsening of aggression or hostility can be caused by treatment with stimulants. Patients treated with methylphenidate should be closely monitored for the emergence or worsening of aggressive behaviour or hostility at treatment initiation, at every dose adjustment and then at least every 6 months and every visit. Physicians should evaluate the need for adjustment of the treatment regimen in patients experiencing behaviour changes.

Suicidal tendency

Patients with emergent suicidal ideation or behaviour during treatment for ADHD should be evaluated immediately by their physician. Consideration should be given to the exacerbation of an underlying psychiatric condition and to a possible causal role of methylphenidate treatment. Treatment of an underlying psychiatric condition may be necessary and consideration should be given to a possible discontinuation of methylphenidate.

Tics

Methylphenidate is associated with the onset or exacerbation of motor and verbal tics. Worsening of Tourette's syndrome has also been reported. Family history should be assessed and clinical evaluation for tics or Tourette's syndrome in children should precede use of methylphenidate. Patients should be regularly monitored for the emergence or worsening of tics during treatment with methylphenidate.

Monitoring should be at every adjustment of dose and then at least every 6 months or every visit.

Anxiety, agitation or tension

Methylphenidate is associated with the worsening of pre-existing anxiety, agitation or tension. Clinical evaluation for anxiety, agitation or tension should precede use of methylphenidate and patients should be **regularly monitored for the emergence or worsening of these symptoms during treatment, at every adjustment of dose and then at least every 6 months or every visit.**

Forms of bipolar disorder

Particular care should be taken in using methylphenidate to treat ADHD in patients with comorbid bipolar disorder (including untreated Type I Bipolar Disorder or other forms of bipolar disorder) because of concern for possible precipitation of a mixed/manic episode in such patients. Prior to initiating treatment with methylphenidate, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. **Close ongoing monitoring is essential in these patients (see above ‘Psychiatric Disorders’ and section 4.2) . Patients should be monitored for symptoms at every adjustment of dose, then at least every 6 months and at every visit.**

Growth

Moderately reduced weight gain and growth retardation have been reported with the long-term use of methylphenidate in children.

The effects of methylphenidate on final height and final weight are currently unknown and being studied.

Growth should be monitored during methylphenidate treatment: height, weight and appetite should be recorded at least 6 monthly with maintenance of a growth chart. Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

Seizures

Methylphenidate should be used with caution in patients with epilepsy. Methylphenidate may lower the convulsive threshold in patient with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and rarely in patients without a history of convulsions and no EEG abnormalities. If seizure frequency increases or new-onset seizures occur, methylphenidate should be discontinued.

Abuse, misuse and diversion

Patients should be carefully monitored for the risk of diversion, misuse and abuse of methylphenidate

Methylphenidate should be used with caution in patients with known drug or alcohol dependency because of a potential for abuse, misuse or diversion.

Chronic abuse of methylphenidate can lead to marked tolerance and psychological dependence with varying degrees of abnormal behaviour. Frank psychotic episodes can occur, especially in response to parenteral abuse.

Patient age, the presence of risk factors for substance use disorder (such as co-morbid oppositional-defiant or conduct disorder and bipolar disorder), previous or current substance abuse should all be taken into account when deciding on a course of treatment for ADHD. Caution is called for in emotionally unstable patients, such as those with a history of drug or alcohol dependence, because such patients may increase the dosage on their own initiative.

For some high-risk substance abuse patients, methylphenidate or other stimulants may not be suitable and non-stimulant treatment should be considered.

Withdrawal

Careful supervision is required during drug withdrawal, since this may unmask depression as well as chronic over-activity. Some patients may require long-term follow up.

Careful supervision is required during withdrawal from abusive use since severe depression may occur.

Fatigue

Methylphenidate should not be used for the prevention or treatment of normal fatigue states.

Excipients: galactose/sucrose intolerance

This medicinal product contains lactose: patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicinal product contains sucrose: patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine

Choice of methylphenidate formulation

The choice of formulation of methylphenidate-containing product will have to be decided by the treating specialist on an individual basis and depends on the intended duration of effect.

Drug screening

This product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test.

Renal or hepatic insufficiency

There is no experience with the use of methylphenidate in patients with renal or hepatic insufficiency.

Haematological effects

The long-term safety of treatment with methylphenidate is not fully known. In the event of Leukopenia, thrombocytopenia, anaemia or other alterations, including those indicative of serious renal or hepatic disorders, discontinuation of treatment should be considered.

Potential for gastrointestinal obstruction

{This wording should be including only in SPCs where it is appropriate, – see wording below :}

Because the *{Invented name}* tablet is nondeformable and does not appreciably change in shape in the gastrointestinal (GI) tract, it should not ordinarily be administered to patients with pre-existing severe GI narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable prolonged-release formulations.

Due to the prolonged-release design of the tablet, *{Invented name}* should only be used in patients who are able to swallow the tablet whole. Patients should be informed that *{Invented name}* must be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction

...[]...

It is not known how methylphenidate may effect plasma concentrations of concomitantly administered drugs. Therefore, caution is recommended at combining methylphenidate with other drugs, especially those with a narrow therapeutic window.

Methylphenidate is not metabolised by cytochrome P450 to a clinically relevant extent. Inducers or inhibitors of cytochrome P450 are not expected to have any relevant impact on methylphenidate pharmacokinetics. Conversely, the d- and l- enantiomers of methylphenidate do not relevantly inhibit cytochrome P450 1A2, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A.

However, there are reports indicating that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g. phenobarbital, phenytoin, primidone) and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). When starting or stopping treatment with methylphenidate, it may be necessary to adjust the dosage of these drugs already being taken and establish drug plasma concentrations (or for coumarin, coagulation times).

Pharmacodynamic interactions

...[]...

Anti-hypertensive drugs

Methylphenidate may decrease the effectiveness of drugs used to treat hypertension.

Use with drugs that elevate blood pressure

Caution is advised in patients being treated with methylphenidate with any other drug that can also elevate blood pressure (see also sections on cardiovascular and cerebrovascular conditions in Section 4.4 Warnings and Precautions for use)

Because of possible hypertensive crisis, methylphenidate is contraindicated in patients being treated (currently or within the preceding 2 weeks) with non-selective, irreversible MAO-inhibitors (see section 4.3 Contraindications).

Use with alcohol

Alcohol may exacerbate the adverse CNS effects of psychoactive drugs, including methylphenidate. It is therefore advisable for patients to abstain from alcohol during treatment.

Use with halogenated anaesthetics

There is a risk of sudden blood pressure increase during surgery. If surgery is planned, methylphenidate treatment should not be used on the day of surgery.

Use with centrally acting alpha-2 agonists (e.g. clonidine)

Serious, adverse events, including sudden death, have been reported in concomitant use with clonidine. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

Use with dopaminergic drugs

Caution is recommended when administering methylphenidate with dopaminergic drugs, including antipsychotics. Because a predominant action of methylphenidate is to increase extracellular dopamine levels, methylphenidate may be associated with pharmacodynamic interactions when co-administered with direct and indirect dopamine agonists (including DOPA and tricyclic antidepressants) or with dopamine antagonists including antipsychotics.

4.6 Pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of methylphenidate in pregnant women.

Cases of neonatal cardiorespiratory toxicity, specifically fetal tachycardia and respiratory distress have been reported in spontaneous case reports.

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses. (See section 5.3)

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

Lactation

Methylphenidate has been found in the breast-milk of a woman treated with methylphenidate

There is one case report of an infant who experienced an unspecified decrease in weight during the period of exposure but recovered and gained weight after the mother discontinued treatment with methylphenidate. A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from methylphenidate therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

...[]...

Methylphenidate can cause dizziness, drowsiness and visual disturbances including difficulties with accommodation, diplopia and blurred vision. It may have a moderate influence on the ability to drive and use machines. Patients should be warned of these possible effects and advised that if affected, they should avoid potentially hazardous activities such as driving or operating machinery.

4.8 Undesirable effects

...[]...

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post-market spontaneous reports with *{invented name}* and those, which have been reported with other methylphenidate hydrochloride formulations. If the ADRs with *{invented name}* and the methylphenidate formulation frequencies were different, the highest frequency of both databases was used.

Frequency estimate:

very common ($\geq 1/10$)

common ($\geq 1/100$ to $< 1/10$)

uncommon ($\geq 1/1000$ to $< 1/100$)

rare ($\geq 1/10,000$ to $< 1/1000$)

very rare ($< 1/10,000$)

not known (cannot be estimated from the available data).

Infections and infestations

Common: Nasopharyngitis

Blood and lymphatic disorders

Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Unknown: Pancytopenia

Immune system disorders

Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders*

Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*

Psychiatric disorders*

Very common: insomnia, nervousness

Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour

Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder

Rare: mania*, disorientation, libido disorder

Very rare: suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focussing,

Not known: delusions*, thought disturbances*, confusional state, dependence.

Cases of abuse and dependence have been described, more often with immediate release formulations (frequency not known)

Nervous system disorders

Very common: headache

Common: dizziness, dyskinesia, psychomotor hyperactivity, somnolence

Uncommon: sedation, tremor

Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit

Neuroleptic malignant syndrome (NMS; Reports were poorly documents and in most of cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).

Not known: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine

Eye disorders

Uncommon: diplopia, blurred vision,

Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*

Common: arrhythmia, tachycardia palpitations

Uncommon: chest pain

Rare: angina pectoris

Very rare: cardiac arrest, myocardial infarction

Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*

Common: hypertension

Uncommon:

Very rare: cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Common: cough, pharyngolaryngeal pain

Uncommon: dyspnoea

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, nausea, stomach discomfort, and vomiting – *{for inclusion in SPCs for non-modified release formulations}*: “these usually occur at the beginning of treatment and may be alleviated by concomitant food intake”, Dry mouth.

Uncommon: constipation

Hepatobiliary disorders

Uncommon: hepatic enzyme elevations

Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders

Common: alopecia, pruritus, rash, urticaria

Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions

Rare: hyperhidrosis, macular rash, erythema

Very rare: erythema multiforme, exfoliative dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia

Uncommon: myalgia, muscle twitching

Very rare: muscle cramps

Renal and urinary disorders

Uncommon: haematuria

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Common: pyrexia, growth retardation during prolonged use in children*

Uncommon: chest pain, fatigue

Very rare: sudden cardiac death*

Not known: chest discomfort, hyperpyrexia

Investigations

Common: changes in blood pressure and heart rate (usually an increase)*, weight decreased*

Uncommon: cardiac murmur*, hepatic enzyme increased

Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

*See Section 4.4 ‘Special warnings and precautions for use’

4.9 Overdose

...[]...

When treating patients with overdose, allowances must be made for the delayed release of methylphenidate from methylphenidate.

Signs and symptoms

Acute overdose, mainly due to overstimulation of the central and sympathetic nervous systems, may result in vomiting, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia,

tachycardia, palpitations, cardiac arrhythmias, hypertension, mydriasis and dryness of mucous membranes.

Treatment

There is no specific antidote to methylphenidate overdose.

Treatment consists of appropriate supportive measures.

The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. If the signs and symptoms are not too severe and the patient is conscious, gastric contents may be evacuated by induction of vomiting or gastric lavage. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. In the presence of severe intoxication, a carefully titrated dose of a benzodiazepine be given before performing gastric lavage.

Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for hyperpyrexia.

Efficacy of peritoneal dialysis or extracorporeal haemodialysis for overdose of methylphenidate has not been established.

Section 5.3 Preclinical safety data

...[]...

Carcinogenicity

In life-time rat and mouse carcinogenicity studies, increased numbers of malignant liver tumours were noted in male mice only. The significance of this finding to humans is unknown.

Methylphenidate did not affect reproductive performance or fertility at low multiples of the clinical dose.

Pregnancy-embryonal/foetal development

Methylphenidate is not considered to be teratogenic in rats and rabbits. Foetal toxicity (i.e. total litter loss) and maternal toxicity was noted in rats at maternally toxic doses.

PACKAGE LEAFLET

1. WHAT METHYLPHENIDATE IS AND WHAT IT IS USED FOR

...[]...

Methylphenidate is used to treat attention deficit hyperactivity disorder (ADHD) in adolescents and children 6 years of age and over when other non pharmaceutical measures alone have proven insufficient.

Methylphenidate should be used together with other forms of treatment, as part of a comprehensive treatment programme. A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with ADHD with symptoms that may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal electroencephalography (EEG). Learning may or may not be impaired. Diagnosis cannot be made solely on the presence of one or more symptom. Adequate diagnosis requires the use of medical and specialised psychological, educational, and social resources.

Methylphenidate must only be initiated by, and used under the supervision of, a specialist in childhood and/or adolescent behavioural disorders

Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and chronicity of the child's symptoms in relation to the child's age. The use of methylphenidate should always be used in this way according to the licensed indication and according to prescribing / diagnostic guidelines.

...[]...

2. Before you take methylphenidate

...[]...

Do not take methylphenidate if you or your child

- are allergic (hypersensitive) to methylphenidate or any of the other ingredients of methylphenidate.
- have glaucoma (increased pressure in the eye)
- have phaeochromocytoma (a tumour of the adrenal gland)
- are taking medicines known as monoamine oxidase inhibitors (MAOIs) for depression, or have taken MAOIs in the last 14 days
- have thyroid problems
- suffer from anorexia nervosa or anorexic disorders
- suffer from depression, mood disorders, mania, or have suicidal thoughts
- suffer from psychotic symptoms or schizophrenia or psychopathic/borderline personality disorder.
- have a diagnosis or history of severe and episodic (Type I) Bipolar (affective) Disorder
- has heart problems such as a history of a heart attack, irregular heartbeat, pain and discomfort in the chest, heart failure, heart disease or significant problems with the structure or function of the heart that were present at birth.
- have a very high blood pressure or narrowing of the vessels, possibly resulting in pain in the arms and legs
- has experienced a cerebrovascular disorder such as stroke, cerebral aneurysm, or vascular abnormalities including cerebral vasculitis

Methylphenidate is not licensed for use in adults with ADHD.

Methylphenidate should not be given to children under 6 years of age or the elderly as the safety and benefits of use in these age groups have not been established.

Take special care with methylphenidate and tell a doctor if you or your child

- Has been told to take these tablets for longer than 12 months (see section 3 below, on long-term use)
- Is entering puberty (teenage years)
- Is about to stop taking methylphenidate as your doctor may want to monitor your child for depression
- has a heart disease or other serious heart problem
- has had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms brain scans)
- has high blood pressure.
- has liver or kidney problems.
- if you or your child has psychiatric disorders .
- has motion or verbal tics (hard-to-control, repeated twitching of any parts of the body or repeated sounds and words)
- is seeing, hearing or feeling things that are not there (hallucinations)
- believes things that are not true (delusions)
- feels unusually suspicious (paranoia)
- experiences mood swings such as racing or impulsive thoughts followed by feeling irritable or emotionally and socially withdrawn
- has suicidal thoughts or actions
- feels depressed or guilty
- feels agitated, anxious or tense
- experiences new or worsening aggressive or hostile behaviour

Tell the doctor before treatment if any of the above conditions or symptoms applies to you or your child.

Checks that your doctor will make before treatment with methylphenidate begins:

In order for your doctor to decide if methylphenidate is the correct medicine for you or your child, your doctor will discuss the following with you:

- about any medications you or your child is taking
- about any other medical conditions (such as heart conditions) you, your child or you family may have.
- whether there is a family history of sudden unexplained death in the family.
- how you or your child are feeling e.g. are you feeling emotional, having strange thoughts or if you have had any of these feelings in the past.
- about any mental health/psychiatric/behavioural problems you or your child or other family members have or have had in the past. Your doctor will specifically discuss whether you or your child is at risk for bipolar (affective) disorder, which will involve checking psychiatric history, including a family history of suicide, bipolar disorder and depression.
- to measure you or your child's height and weight, heart rate and blood pressure and will record these on a chart
- whether there is a family history of tics

It is important that you provide all information so your doctor can decide if methylphenidate is the correct medicine for you or your child. Your doctor may decide you or your child need other medical tests before you or your child take this medicine.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you or your child is taking other medicines, methylphenidate may affect how well other medicines work or may cause side effects. If you or your child is taking any of the following medicines, check with the doctor before taking methylphenidate:

- Non-selective, irreversible, monoamine oxidase (MAO) inhibitors (used to treat depression)
- Vasopressor agents (drugs which may increase blood pressure)
- Medicines used to reduce the blood pressure, for example clonidine, guanethidine, verapamil, propranolol, etc.
- Some cough and cold remedies which contain ingredients that can affect blood pressure, so it is important to check with your pharmacist when you buy any of these products.
- Medicines for depression, including amitriptyline, imipramine and fluoxetine, paroxetine
- Medicines for epilepsy (anticonvulsants) (e.g. phenobarbital, phenytoin, primidone, etc)
- medicines that thin the blood to prevent blood clots (blood thinners, e.g. warfarin)
- dopaminergic drugs, including antipsychotics

If surgery is planned using a halogenated anaesthetic (a certain type of anaesthetic), you or your child should not take methylphenidate on the day of surgery, due to the risk of a sudden rise in blood pressure during surgery.

Drug testing

This medicine may give a positive result when testing for drug use.

If you are in any doubt about whether any medicines you or your child is taking are included in the list above, ask your doctor or pharmacist before taking

methylphenidate.

{For inclusion in the PL of non-modified release formulations of methylphenidate:}

“Taking methylphenidate with food and drink

Taking methylphenidate with food may help relieve stomach pains, feeling sick or vomiting.”

Taking methylphenidate with alcohol

You or your child must not drink alcohol while taking this medicine as alcohol may make this medicine’s side effects worse. Remember that some foods and medicines contain alcohol.

Pregnancy and breast-feeding

Tell your doctor or pharmacist before using methylphenidate if you or your child is:

- sexually active. Your doctor will discuss contraception with you.
- pregnant or think you may be pregnant. Your doctor will decide whether you or your daughter should use methylphenidate.
- breast-feeding or planning to breast-feed. There is limited information that suggests that methylphenidate is passed into human breast milk. Therefore, your doctor will decide whether you or your daughter should breast-feed while using methylphenidate.

Driving or using machines

Dizziness, drowsiness and visual disturbances may occur when taking methylphenidate. If such side-effects occur it may be dangerous to perform any hazardous activities, such as driving, operating machinery, riding a bike or climbing trees until you are certain that you or your child will not be affected.

Important information about some of the ingredients of methylphenidate

{To be completed nationally, as appropriate}

...[]...

3. HOW TO <TAKE> <USE> methylphenidate

...[]...

Before you start treatment, at every change of dose and then at least every 6 months or every visit your doctor will conduct various tests to make sure that methylphenidate is still acceptably safe and beneficial. These will include:

- Measuring blood pressure and heart rate and recording these on a chart, each time your dose in changed and then at least every six months or at every visit.
- Measuring height, weight and appetite recording these on a chart, each time your dose in changed and then at least every six months or at every visit.
- Assessing psychiatric symptoms, each time your dose in changed and then at least every six months or at every visit.

Dose titration

Careful dose titration is necessary at the start of treatment with methylphenidate. Dose titration should be started at the lowest possible dose.

<Always <take> <use> methylphenidate exactly as your doctor has told you. You should check with your <doctor> <or> <pharmacist> if you are not sure.> <The usual dose is...>

If you or your child do not feel better with this medicine, your doctor may decide a different treatment is needed. Tell the doctor if there is no improvement in your child's condition after 1 month of treatment with methylphenidate.

Long-term treatment

Methylphenidate treatment does not need to be indefinite. If methylphenidate is taken for more than a year, your doctor should stop your treatment with methylphenidate for a short time once a year to see if the medicine is still needed. You or your child may continue to see a benefit when methylphenidate is either temporarily or permanently stopped. This may happen during school holidays.

Patients on long-term therapy (i.e. over 12 months) must have careful ongoing monitoring, especially for . or cardiovascular status, growth, appetite, development of *de novo* or worsening of pre-existing psychiatric symptoms

Abuse

Your child should be monitored for the risk of diversion, misuse and abuse of methylphenidate. Longstanding abuse of methylphenidate can lead to marked tolerance, psychological dependence, abnormal behaviour, psychotic episodes. This medicine is intended solely for you or for your child. It must only be prescribed by a doctor and must therefore not be passed on to anyone else. It may harm other people, even if they have the same symptoms as your child

If you <take> <use> more methylphenidate than you should

If you or your child takes too many tablets, contact the doctor or nearest hospital casualty department immediately and tell them how many tablets have been taken.

Signs of overdose may include: vomiting, agitation, shaking, increased uncontrolled movements, muscle twitching, fits (may be followed by coma), feeling of extreme happiness, confusion (severe confusion), hallucinations (seeing, feeling or hearing things that are not real), sweating, flushing, headache, high fever, changes in heart beat (slow, fast or irregular), high blood pressure, dilated pupils and dry nose and mouth.

If you forget to <take> <use> methylphenidate

<you or your child should take the next dose when it is due. Never take a double dose to make up for a forgotten <tablet> <dose> <...>.>

If you stop <taking> <using> methylphenidate

Administration of the tablets should not stop abruptly. You should closely follow the advise of your doctor. Careful supervision is required during withdrawal as this may unmask depression, as well as chronic over-activity.

<If you have any further questions on the use of this product, ask your <doctor> <or> <pharmacist>.>

4. POSSIBLE SIDE EFFECTS

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

The likelihood of having a side effect is as follows:

Very common (more than 1 out of 10 persons)

Common (more than 1 out of 100 persons and less than 1 out of 10 persons)

Uncommon (more than 1 out of 1,000 persons and less than 1 out of 100 persons)

Rare (more than 1 out of 10,000 persons and less than 1 out of 1,000 persons)

Very rare (less than 1 out of 10,000 persons)

Not known (cannot be estimated from the available data).

The most common side effects are nervousness, sleeplessness and headache.

Some side effects could be **serious**. If you suffer from or have any worries about any of the the side effects below, **tell your doctor or pharmacist**:

- severe changes in mood or personality
- mania
- psychotic disorders, including visual, tactile or auditory hallucinations or delusions
- palpitations, unexplained fainting chest pain, shortness of breath (these can sometimes be signs of cardiac disease)
- paralysis or impairment of movement and vision, difficulties in speech (could be symptoms of cerebral vasculitis).

Effects on growth and maturation

When used for a long period of time, methylphenidate may cause reduced growth (weight gain and/or height) in some children. Your doctor will therefore carefully be watching you or your child's height and weight. as well as how well you or your child is eating. If you or your child is not growing or gaining weight as expected, then you or your child's treatment with methylphenidate may be stopped for a short time

Other side effects include:

Infections and infestations

Common: Nasopharyngitis

Blood and lymphatic disorders

Very rare: Anaemia, leukopenia, thrombocytopenia, thrombocytopenic purpura

Unknown: Pancytopenia

Immune system disorders

Uncommon: hypersensitivity reactions such as angioneurotic oedema, anaphylactic reactions, auricular swelling, bullous conditions, exfoliative conditions, urticarias, pruritis, rashes and eruptions

Metabolism and nutritional disorders*

Common: anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children*

Psychiatric disorders*

Very common: insomnia, nervousness

Common: anorexia, affect lability, aggression*, agitation*, anxiety*, depression*, irritability, abnormal behaviour

Uncommon: psychotic disorders*, auditory, visual, and tactile hallucinations*, anger, suicidal ideation*, mood altered, mood swings, restlessness, tearfulness, tics*, worsening of pre-existing tics or Tourette's syndrome*, hypervigilance, sleep disorder

Rare: mania*, disorientation, libido disorder

Very rare: suicidal attempt (including completed suicide)*, transient depressed mood*, abnormal thinking, apathy, repetitive behaviours, over-focussing,

Not known: delusions*, thought disturbances*, confusional state

Nervous system disorders

Very common: headache

Common: dizziness, dyskinesia, psychomotor hyperactivity, somnolence

Uncommon: sedation, tremor

Very rare: convulsions, choreo-athetoid movements, reversible ischaemic neurological deficit

Neuroleptic malignant syndrome (NMS; Reports were poorly documents and in most of cases, patients were also receiving other drugs, so the role of methylphenidate is unclear).

Not known: cerebrovascular disorders* (including vasculitis, cerebral haemorrhages, cerebrovascular accidents, cerebral arteritis, cerebral occlusion), grand mal convulsions*, migraine

Eye disorders

Uncommon: diplopia, blurred vision,

Rare: difficulties in visual accommodation, mydriasis, visual disturbance

Cardiac disorders*

Common: arrhythmia, tachycardia palpitations

Uncommon: chest pain

Rare: angina pectoris

Very rare: cardiac arrest, myocardial infarction

Not known: supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles

Vascular disorders*

Common: hypertension

Uncommon:

Very rare: cerebral arteritis and/or occlusion, peripheral coldness, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders

Common: cough, pharyngolaryngeal pain

Uncommon: dyspnoea

Gastrointestinal disorders

Common: abdominal pain, diarrhoea, nausea, stomach discomfort, and vomiting – *{for inclusion in PL for non-modified release formulations :}* “these usually occur at the beginning of treatment and may be alleviated by concomitant food intake”, Dry mouth.

Uncommon: constipation

Hepatobiliary disorders

Uncommon: hepatic enzyme elevations

Very rare: abnormal liver function, including hepatic coma

Skin and subcutaneous tissue disorders

Common: alopecia, pruritus, rash, urticaria

Uncommon: angioneurotic oedema, bullous conditions, exfoliative conditions

Rare: hyperhidrosis, macular rash, erythema

Very rare: erythema multiforme, exfoliative dermatitis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia

Uncommon: myalgia, muscle twitching

Very rare: muscle cramps

Renal and urinary disorders

Uncommon: haematuria

Reproductive system and breast disorders

Rare: Gynaecomastia

General disorders and administration site conditions

Common: pyrexia, growth retardation during prolonged use in children*

Uncommon: chest pain, fatigue

Very rare: sudden cardiac death*

Not known: chest discomfort, hyperpyrexia

Investigations

Common: changes in blood pressure and heart rate (usually an increase)*, weight decreased*

Uncommon: cardiac murmur*, hepatic enzyme increased

Very rare: blood alkaline phosphatase increased, blood bilirubin increased, platelet count decreased, white blood count abnormal

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.

...[]...

ANNEX IV
CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATIONS

National Competent Authorities, coordinated by the Reference Member State where applicable, shall ensure that the following conditions are fulfilled by the Marketing Authorisation Holders:

Product Information

Package Leaflet

The MAHs should harmonise the relevant wording of the Package Leaflet by reflecting the changes proposed in the SPC. The PL wording agreed by the CHMP should be revised to improve patient readability, and will then be user-tested.

Cardiovascular and Cerebrovascular effects

Study designed to:

- 1) assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in children and youth, aged 2-24 years;
- 2) assess the relationship between use of medications for ADHD and the risk of serious cardiovascular disease in adults, aged 25-64 years; and,
- 3) perform additional analyses that are relevant to decision makers such as clinicians, state Medicaid programs, and parents/patients.

The MAHs will evaluate the final report of the study, when published, and will update the Core RMP, and where appropriate the Core SPC/PL, to reflect the findings.

Cytogenicity

Study CRIT124D2201 “*An open label, behavioural treatment controlled evaluation of the effects of extended release methylphenidate (Ritalin LA) on the frequency of cytogenetic abnormalities in children 6-12 years old with attention deficit hyperactivity disorder*”. The Core RMP, and where appropriate the Core SPC/PL, should be updated to reflect the findings of this study.

Study NCT 00341029 “*Measurement of Cytogenetic Endpoints in Lymphocytes of Children Diagnosed With Attention Deficit/Hyperactivity Disorder (ADHD) and Treated With Methylphenidate or Adderall*”, carried out by US National Institute of Environmental Health Sciences in collaboration with FDA. The MAHs will evaluate the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings:

Growth, Development and Sexual Maturation

MTA Study. “*Effects of stimulant medication on growth in the MTA (Multimodal Treatment Study of ADHD)*” follow-up, carried out by the MTA Cooperative Group. The MAHs will evaluate the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings.

Study on sexual maturation: a 2-year, long-term, open-label, prospective investigator initiated study in the US on 150 adolescents (12-17 years) with ADHD, to determine whether treatment with methylphenidate will prevent smoking in this population. Although the study focuses on smoking prevention, Tanner staging examinations will occur every 6 months during the 2-year follow-up and will monitor each subject's pubertal development to demonstrate whether methylphenidate has any effect on adolescent growth and development compared to population norms. The MAHs will make available the final report of the study, when published, and will update the RMP, and where appropriate the SPC/PL, to reflect the findings.

Psychiatric effects

The MAHs will investigate the feasibility of carrying out a meta-analysis of the risk of suicidality associated with the use of methylphenidate in children and adolescents with ADHD on the basis of the clinical trial data of methylphenidate that is currently available to the MAHs.

If the analysis on the basis of the currently available data is deemed feasible, the MAHs will make the resources available to support the analysis and update the RMP to reflect its findings.

Long Term Use effects

The MAHs committed to provide a detailed feasibility assessment for a scientifically valid, well-designed and suitably powered long-term safety study to examine specific endpoints for the following outcomes:

- i) adverse cognitive outcomes
- ii) adverse psychiatric outcomes (e.g. mood disorders, hostility and psychotic disorders)

The MAHs will consider including predominantly EU-based data, and the feasibility assessment will also comment on what non-EU sources of data could be used as an alternative. If the feasibility assessment shows that a scientifically valid, well-designed and suitably powered study is viable, then the MAHs commit to provide a detailed protocol. The proposed follow-up duration of at least 5 years for individual subjects will be considered. Within the 5-year follow-up, particular emphasis will be placed on assessing the effects of a cumulative exposure of at least 18 months. Because this is a non-interventional study, the MAH's will have no control over actual prescribing practices. The proposed patient enrolment age will be as young as possible consistent with the age restrictions of the label (i.e. children aged 6 years or more). The preferred design would be a prospective, cohort study. The MAHs agree to evaluate suitable comparator groups.

Drug utilisation studies, including evaluation of Off-Label Use/ Abuse

The MAHs commit to provide all available retrospective data on an annual review basis for the next five years in all Member States where methylphenidate is used, to allow an evaluation of changes in usage over time. Where possible, measures of usage including variables such as information on total amount used, patient age, gender, indication dose, duration of use, treatment continuity, co-morbidities, concomitant medications, data on patterns of use, physician specialty will be used. This commitment will be reviewed after 5 years.

In the Member States that are covered by the IMS database, the MAHs will also evaluate off-label use of methylphenidate. The MAHs will also consider alternative methods for completing the review of usage (where possible) and off-label use in the Member States that are not currently covered by multi-national (EU-wide) databases such as IMS.

Educational tools

The MAHs will produce fully harmonised Risk Minimisation tools that contain all of the important information from the Clinical Particulars section of the Core SPC. :

- Physicians guide to prescribing
- Checklists for actions before prescribing, and for ongoing monitoring for prescribers and, if possible, carers

PSURs

The MAHs will harmonise the PSUR reporting schedule for methylphenidate-containing products and submit once yearly PSURs for their respective products for the next 3 years, after which the reporting frequency will be reviewed. The synchronisation of the PSUR submission will facilitate a common assessment and harmonised response by the National Competent Authorities on updates of the SPC / PL and RMP.

Risk Management Plans

The MAHs should include, in the core safety specification, the final core table of identified and potential risks as requested by the CHMP.

The MAHs should evaluate newly identified or potential risks, or new new/important information on existing identified or potential risks, in the RMP on an ongoing basis