**[SCHEDULE Y](http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf)**

**Form 44**

**(See rules 122 A, 122 B, 122 D, and 122 DA)**

Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial.

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I/we **Dr. Papa Dasari, Professor, Department of Obstetrics & Gynaecology, JIPMER,** hereby apply for grant of permission for clinical trial of already approved drug, but for new indication. The necessary information / data is given below:

**Particulars of New Drug:**

(1) **Name of the drug** : **METFORMIN**

(2) **Dosage Form** : oral tablet

(3) **Composition of the formulation:**

Drug will be purchased by the patient. The drug will be used as such without any modification.

(4) **Test specification**:

Active ingredients:

* + - Metformin hydrochloride (1000 mg)

(N,N dimethylimidodicarbonimidic diamide hydrochloride).

* + - Methylcobalamine (750 mcg)

(5) **Pharmacological classification of the drug:** Oral Hypoglycaemic Agents (Biguanide)

(6) **Indications for which proposed to be used:** Gestational Diabetes Mellitus

(7) **Manufacturer of the raw material (bulk drug substances):** Not Applicable.

(8**) Patent status of the drug:** Both generic and branded forms are available in the market.

Data submitted along with the application (as per Schedule Y with indexing and page nos.)

A. **Permission to market a new drug:**  NOT APPLICABLE.

B. **Subsequent approval / permission for manufacture of already approved new drug:** NOT APPLICABLE. (As, we do not intend to manufacture any drug).

C. **Approval / Permission for fixed dose combination:** NOT APPLICABLE

D. **Subsequent Approval or approval for new indication – new dosage form:**

1. **Number and date of Approval/permission already granted** – Metformin appears in the ‘National list of Essential Medicines of India- 2011’ (Section 18.5 under Hormones, Other Endocrine Medicines and Contraceptives).

(2) **Therapeutic Justification for new claim / modified dosage form**

**Therapeutic justification:**

India is considered to be the capital of Diabetes mellitus. Pregnancy is a potentially glucose intolerant condition. GDM increases the risk of certain pregnancy complications like abortion, pregnancy induced hypertension, polyhydramnios, preterm labour and adverse perinatal outcome such as congenital malformations, macrosomia, sudden intrauterine death. The main purpose of treatment is to prevent hyperinsulinemia and fetal complication by reducing maternal glucose levels. This is initially attempted by dietary advice, but women often require additional treatment, which has traditionally been insulin 1. When diet control fails, Insulin therapy is initiated. It is costly and requires skill to administer and requires special storage conditions like refrigeration. Women in developing countries may not comply with such treatment. Further, it causes hypoglycaemia when it is not properly administered or when adequate diet is not consumed along with it.

Oral hypoglycaemic agents (OHA) are as efficient as insulin and provide better quality of life though fear of congenital malformations still exists. Metformin, a biguanide, a Class B drug 2, decreases hepatic gluconeogenesis, glucose absorption, improves peripheral glucose uptake by increasing insulin sensitivity3. It does not cause hypoglycaemia and not associated with appreciable weight gain. Hence it can be safely administered during pregnancy. There is a controversy regarding its usage during pregnancy as it crosses the placenta and some studies have reported it being associated with increased incidence of preeclampsia 4 and adverse perinatal outcome though others did not find any such association 1,5,6.

(3) **Data generated on safety, efficacy and quality parameters:**

**Efficacy data :**

In the year 2000, Hellmuth E and colleagues published a retrospective cohort study which evaluated the role of OHAs in GDM and in type 2 Diabetes mellitus during pregnancy. They evaluated the outcome using Tolbutamide (n =65) for normal weight women and metformin (n=50) for overweight women. They concluded that metformin was associated with increased prevalence of preeclampsia and high perinatal mortality. This may be due the difference in BMI and other risk factors of the study subjects 4.

In the year 2004 Gluecks and colleagues conducted a prospective observational study in 42 pregnant women who conceived following treatment with metformin for Polycystic Ovarian Syndrome. Metformin therapy was continued during first trimester and also throughout pregnancy. Only 7% of those 42 women developed gestational diabetes. They concluded that metformin reduces the development of GDM by improving the Insulin sensitivity. They proved this by estimating HOMA IR during pre-pregnancy, 1st trimester, 2nd trimester and also during 3rd trimester 8.

An Indian study from Manipal which compared the use of Metformin and Insulin in GDM and type 2 DM during pregnancy in 60 women has concluded that metformin is effective, cheap and a safe alternative to insulin therapy in pregnant women 6.

A review by Renda E and colleagues in 2011 addressed the treatment options for GDM with regards to oral hypoglycaemic agents or Insulin which stated that the glyburide and metformin had similar or better neonatal outcomes when compared to insulin. However still controversy exists regarding the use of OHA in GDM and further follow up data are needed to establish the long term safety 3.

A Meta analysis including 5 RCTs addressing the same issue in 2013 concluded that metformin comparable to insulin in the management of GDM and management guidelines need to be developed regarding its usage in GDM 9.

**Safety data:**

FDA and NICE Guidelines has approved its use in Type 2 Diabetes Mellitus. However due to lack of experience of use in pregnancy, it has been classified under Category B. Safety data in humans are provided below:

Rowan JA in 2009, conducted a RCT, metformin versus insulin for the treatment of GDM in 751 women between 20 to 33 weeks. They concluded that metformin did not increase the perinatal complications when compared to insulin and there was no statistically significant difference in other secondary outcomes like maternal glycaemic control and gestational hypertension between the two groups. Significantly more number of women preferred metformin therapy 5.

A Retrospective cohort study from our own Institute which was published in 2011 found 90% of pregnant women can achieve glycaemic control with metformin at a dose of 1500gm/ day. There were no cases of maternal and neonatal hypoglycaemia and no congenital malformations as metformin was employed in 24% during first trimester 10.

This protocol has been approved by JIPMER scientific Advisory Committee. We have submitted the protocol for Institute Ethics committee approval and they also have approved.

A total fee of rupees \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (in words). \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_) has been credited to the Government under the Head of Account \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (Photocopy of receipt is enclosed).

**Request for waiver of fees:**

Since this is a purely academics oriented study done in a government hospital with a good intention to help the patients in need without any commercial interest, we request you to kindly exempt us from paying the registration fees.

Dated: 13/07/2015 Signature: D. Papa

Designation: Professor

Note- Delete, whichever is not applicable.

**REFERENCES:**

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9. Gui J, Liu Q, Feng L. Metformin vs Insulin in the Management of Gestational Diabetes: A Meta-Analysis. PLoS ONE 2013;8(5): e64585. doi:10.1371/journal.pone.0064585.
10. Papa D, Habeebullah S. Maternal and fetal outcome in Gestational Diabetes Mellitus Treated with Diet and Metformin – A Preliminary Retrospective Analysis. The Open Conference Proceedings Journal. 2011;2:59-63.
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