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RevAssist®

A Comprehensive Risk Minimization Programme for Preventing Fetal Exposure to Lenalidomide

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Abstract

Lenalidomide (Revlimid®) is an immunomodulatory drug and an analogue of thalidomide, a known teratogen. To prevent fetal exposure, in the US lenalidomide is available only under a special restricted distribution programme called RevAssist®. Under this risk minimization programme, only prescribers and contract pharmacies registered with the programme are able to prescribe and dispense the product. Patients must be advised of, agree to and comply with the requirements of the RevAssist® programme in order to receive lenalidomide through a registered prescriber. A total of 15 584 patients were registered in the RevAssist® programme during the first year lenalidomide was on the market. There were four reports of false-positive β-human chorionic gonadotrophin measurements in patients aged 43–57 years. Mandatory patient and prescriber

surveys have shown discrepant responses that were resolved by risk management intervention specialists 99% of the time. The voluntary patient surveys have shown understanding of the risks of lenalidomide use and of behaviours necessary to minimize risks in >95% of females of childbearing potential and adult males. To date, there have been no reports of pregnancy in female patients or female partners of male patients. The pharmacy audit findings showed compliance with RevAssist® was high. Although RevAssist® is labour-intensive, time-consuming and costly, it continues to be effective in preventing fetal exposure to lenalidomide.

Lenalidomide (Revlimid® [1]) is approved in the US for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality (with or without additional cytogenetic abnormalities), and in combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.

Lenalidomide is an analogue of thalidomide, a known human teratogen that causes severe developmental deformities, including phocomelia. Lenalidomide is rapidly absorbed following oral administration, with maximum plasma concentrations occurring between 0.625 and 1.5 hours post-dose. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The elimination half-life is approximately 3 hours.[1]

Preclinical developmental toxicity studies in rabbits have shown that thalidomide causes multiple endpoints of developmental toxicity, including congenital malformations not always observed in other species. Recent studies in the New Zealand white rabbit have failed to demonstrate malformations in fetuses exposed to lenalidomide.[2] Nonetheless, because of the structural similarity between lenalidomide and thalidomide, in the US the drug is only available under a special restricted distribution programme called RevAssist®, which was developed in conjunction with the US FDA. The programme's primary goal is to prevent fetal exposure among female patients of childbearing potential (FCBP) and females who may be impregnated by male patients receiving lenalidomide.

Risk minimization programmes are recommended by the FDA and developed by pharmaceutical manufacturers to optimize the benefit-risk balance of a particular medicinal product. The development and utilization of these risk minimization programmes entail an iterative process of risk assessment,[3] risk minimization[4] and evaluation of effectiveness[5] to further improve the benefit-risk balance.[6] The RevAssist® programme is a risk minimization programme that was modelled after the System for Thalidomide Education and Prescribing Safety (STEPS®).[7] The principal components of RevAssist® include:

1. affixed signatures in the physician-patient agreement form (PPAF) from both the physician and the patient;
2. controlled access through registration of prescribers, patients and contract pharmacies;
3. mandatory education of patients, prescribers and pharmacists about the risk associated with lenalidomide therapy;
4. a requirement for adequate contraceptive measures (at least one highly effective method and one

1 The use of trade names is for product identification purposes only and does not imply endorsement.

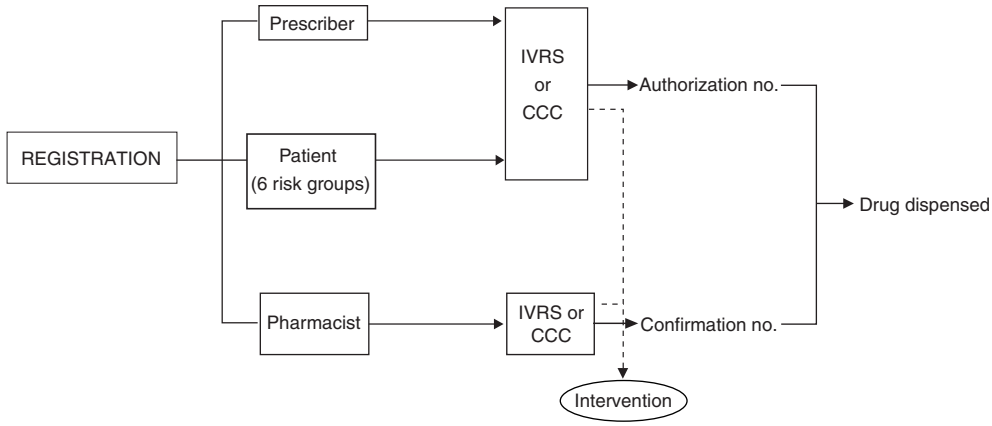

Fig. 1. Overview of the procedures in the RevAssist® programme. *Prescriber:* a licensing practitioner and registered in RevAssist®. The prescriber calls the interactive voice response system (IVRS) or customer care centre (CCC) and responds to the mandatory survey questions. The prescriber obtains an authorization number that is provided after the patient has completed the mandatory patient survey and is faxed to the pharmacist. *Patient:* a person prescribed lenalidomide and registered with RevAssist®. The patient calls the IVRS or CCC and responds to mandatory survey questions. *Pharmacist:* A pharmacy registered with RevAssist® who will dispense lenalidomide. The pharmacist calls the IVRS or CCC to obtain the confirmation number. The pharmacist contacts the patient to provide counselling and dispenses a 28-day supply of lenalidomide. *Risk groups:* (i) adult female of childbearing potential; (ii) adult female not of childbearing potential; (iii) female child of childbearing potential; (iv) female child not of childbearing potential; (v) adult male; and (vi) male child. *Intervention:* Responses to the mandatory patient and prescriber surveys that are discrepant or inappropriate are transferred to the Risk Intervention Specialist who evaluates and helps to resolve the discrepant or inappropriate response.

additional effective method) for FCBP and adult males;

5. controlled distribution through contract pharmacies;

6. pregnancy tests before, during and after treatment among FCBP;

7. monitoring of compliance through mandatory prescriber and patient surveys.

The evaluation of the effectiveness of the programme is undertaken through the voluntary patient surveys and pharmacy audits. Figure 1 provides an overview of the procedures in the RevAssist® programme. To complement the programme, a pregnancy exposure registry was also put in place to monitor the outcome of any pregnancies that occur during the use of lenalidomide and to understand the reason for failure of the programme.

Lenalidomide is currently one of eight drugs with a mandatory limited distribution system in the US. Four of these drugs (lenalidomide, thalidomide, bosentan and isotretinoin) have pregnancy prevention risk minimization programmes (RevAssist®, STEPS,[7,8] Tracleer® Access Programme [TAP][9] and iPLEDGE,[10] respectively). Currently, all of these programmes share certain common methods that include education of patients and prescribers, patient consent, controlled distribution and mandatory pregnancy testing.

The continuous evaluation of the effectiveness of the risk minimization programme is important to achieve the primary goal of preventing fetal exposure to lenalidomide. We are not aware of any of the above pregnancy prevention programmes that have published results of the evaluation of the programme performance relative to preventing fetal exposure. The purpose of this report is to present the results of the mandatory surveys and the evaluation of the effectiveness of RevAssist® in preventing fetal exposure among FCBP and adult males during its first year in the commercial environment in the US.

1. Methods for Assessing Programme Effectiveness

1.1 Mandatory Patient and Prescriber Survey

Patients complete the mandatory Patient Survey based on their risk category: (i) adult FCBP; (ii) adult female not of childbearing potential; (iii) female child of childbearing potential; (iv) female child not of childbearing potential; (v) adult male; and (vi) male child. An FCBP is defined as a sexually mature female who has not undergone a hysterectomy, bilateral oophorectomy, or who has not been postmenopausal for at least 24 consecutive months (i.e. who has had menses at some time in the preceding 24 consecutive months). A female child of childbearing potential is defined as a sexually or not sexually active menstruating female <18 years of age.

The mandatory surveys are completed by the prescribers every time a prescription is written and every month by the patients via the interactive voice response system (IVRS) or customer care centre (CCC). The mandatory prescriber surveys include questions on contraception counselling, pregnancy testing and lenalidomide prescription (i.e. dose and duration). The mandatory survey for FCBP and adult males includes questions on the use of birth control methods and drug sharing, and includes an additional question on menstrual periods for FCBP. A pre-set computer algorithm identifies discrepant responses to the questions. Discrepant responses are defined in two ways: (i) discrepancies between patient and prescriber responses; and (ii) responses that diverge from the desired answers.

1.2 Voluntary Patient Survey

For the voluntary survey, samples of patients are selected from each of the non-FCBP risk groups, proportional to their representation in the overall population of registered patients, in addition to all FCBP who have been dispensed lenalidomide. A stratified random patient sample is selected every week from the cumulative database of those patients who indicated willingness to participate in a voluntary survey when they filled in the PPAF. Two samples of patients are included: patients newly prescribed lenalidomide (phase 1) and patients who have been receiving lenalidomide for at least 3 months (phase 2). Phase 1 evaluates the understanding of the risks of lenalidomide use and behaviours necessary to minimize risks. The survey includes questions on the patient's knowledge of birth control methods, birth defects, lenalidomide use and pregnancy prevention. The phase 1 survey forms are mailed to all FCBP and selected patients within 14 days of lenalidomide being dispensed.

Phase 2 uses a repeated cross-sectional sampling design and monitors retention of knowledge and compliance with the methods of contraception and appropriate risk reduction behaviours. Patients who have had more than one prescription refilled and who have been receiving lenalidomide for a minimum of 3 months are sampled. While the sample is drawn from the same population as in phase 1, it does not necessarily include the same individuals. The sampling frame is evaluated every 6 months based on the representation of new and continuing patients in the RevAssist® database. The survey is administered by mail questionnaire or by telephone interview, and survey questionnaires are specific for each patient risk category. Patients who do not respond are contacted by telephone and are classified as nonresponders after three attempts of telephone contact without any response. Survey data were collected and analysed by a contract research organization. A compliant FCBP is defined as a FCBP who is either (i) abstinent from sex; (ii) using two primary methods of contraception; (iii) using one primary method and a barrier method of contraception; (iv) menopausal and >50 years of age; or (v) not sexually active with no plans to become

sexually active. A compliant male is defined as a male who is either (i) abstinent from sex; (ii) using a condom; (iii) engaged with a menopausal partner; or (iv) not sexually active with no plans to become sexually active.

1.3 Pharmacy Audits

Pharmacy audits are conducted periodically by Celgene Compliance and Quality Management group. The RevAssist® audit programme ensures that all RevAssist® controls have been implemented as designed and are working effectively. Control categories are defined based on potential risk of fetal exposure, and include control areas such as pharmacy counsellor training, prescription and counselling accuracy, pharmacy dispensing controls, adverse event reporting and drug accountability.

1.4 Pregnancy Test Results

In addition to the mandatory prescriber survey, the prescribers are required to report abnormal pregnancy test results to Celgene Drug Safety.

To fully evaluate the effectiveness of the RevAssist® programme, a review of patient information from the database of the RevAssist® programme and pregnancy test results from the Celgene safety database was undertaken. The timeframe of observation in this report covers the period from the approval of lenalidomide on 27 December 2005 through to 31 December 2006.

2. Evaluation of Effectiveness

2.1 Registered Patients in RevAssist®

During the period 27 December 2005 to 31 December 2006, a total of 15 584 patients were registered in the RevAssist® programme. Of the registered patients, 93% were prescribed lenalidomide for the approved indications of myelodysplastic syndromes (MDS) and multiple myeloma. Approximately 39% of the patients were prescribed lenalidomide for MDS and 54% were prescribed lenalidomide for multiple myeloma. A slight majority (56%; 8721/15 584) of all registered patients were males. There were 324 FCBP, comprising 2.1% of all registered patients and 4.7% of all female patients. The risk category 'female not of childbearing potential' accounted for 41.9% (6534/15 584) of all registered patients. Table I presents the distribution of registered patients by risk classification.

2.2 Mandatory Patient and Prescriber Surveys

Registered FCBP patients and prescribers completed 1593 mandatory surveys, while registered male patients and prescribers completed 28 375 mandatory surveys. The computer algorithm identified discrepant responses between FCBP and prescriber to the mandatory survey questions regarding natural menopause and surgical removal of the uterus (table II). A slightly greater number of prescribers than patients responded positively to the survey questions that their patients had natural menopause or had surgical removal of the uterus. Mandatory survey questions with responses that diverged from the desired answers include the use of two birth control methods during sexual intercourse for both the males and FCBP, and pregnancy testing and male patient reminder to use latex condoms during sexual activity for the prescribers (table III). The mandatory survey question with the most number of

Table I. Distribution of registered patients by risk category

Risk category	No. of patients (%)
Females of childbearing potential	324 (2.1)
Females not of childbearing potential	6 534 (41.9)
Male adults	8 721 (56.0)
Male children <18 years	5 (0.0)
Total no. of registered patients	15 584

Table II. Mandatory survey questions with discrepant responses (i.e. those responses with disagreement between the prescriber and the patient) between female patients of childbearing potential (FCBP) and prescriber

Survey question	FCBP (n)	Prescriber (n)
FCBP: Have your menstrual periods stopped naturally for more than 24 months? Prescriber: Has the patient experienced a natural menopause for at least 24 months?	170	226
FCBP: Have you had your womb or uterus surgically removed? Prescriber: Has the patient had her womb or uterus surgically removed?	138	189

responses that diverged from the desired answers was the date of the pregnancy test.

2.3 Voluntary Patient Surveys

During phase 1, a total of 8623 patients agreed to participate in the voluntary patient surveys; of these, 2849 were selected for the survey and 2131 (74.8%) responded to the survey questions. During phase 2, a total of 4539 patients agreed to participate in the survey; of these, 2219 were selected for the survey and 1657 (74.7%) responded to the survey questions. Table IV provides the distribution of voluntary survey respondents by risk category. There is a marked decrease in the number of FCBP respondents in phase 2.

Table III. Mandatory survey questions with divergence from the desired answers

Survey question	N
FCBP survey (n = 1593)	
In the past 4 weeks, have you had sexual intercourse with a male partner? If the answer is Yes,	
On any occasion during the last 4 weeks, have you had sexual intercourse without using two forms of birth control?	19
Male survey (n = 28 375)	
Are you sexually active with a woman who has her womb, is pregnant, or could become pregnant? If the answer is Yes,	
While taking Revlimid®, have you used a latex condom every time you have engaged in sexual activity with a female who is or could become pregnant?	13
Prescriber survey for FCBP	
What is the date of the most recent pregnancy test?	179
What was the result of the pregnancy test?	21
Prescriber survey for males	
Have you reminded the patient or his guardian that a latex condom must be used every time he engages in any sexual activity with a female who is or could become pregnant?	52

FCBP = female patients of childbearing potential.

The majority of the respondents were ≥40 years old. The median ages for FCBP were 47 and 48 years in phase 1 and 2, respectively; for males they were 68 and 67 years in phase 1 and 2, respectively.

Table V provides the distribution of responses to receipt of the patient information brochure and pharmacist counselling on lenalidomide during phase 1. The majority of the FCBP reported getting the brochure, reading it and having interactions with pharmacists, which included lenalidomide information. Male adults similarly reported receiving and reading the brochure, but reported less pharmacist interaction.

More than 95% of FCBP and adult males understood the risks associated with lenalidomide and responded correctly to the questions related to preventing fetal exposure. Table VI provides the distribution of responses to key knowledge questions among FCBP and adult males.

The most commonly reported method of birth control among FCBP in both phases was the use of condoms. Among males, abstinence was the most commonly reported method of birth control in phase 1. Twenty percent of the males reported infertility in their partner due to menopause or hysterectomy in phase 2. Table VII provides the distribution of birth control use by risk category.

The phase 2 survey contains behavioural questions such as the use of birth control methods since start of lenalidomide, number of concurrent birth control methods used, use of emergency contraception and frequency of using one or two methods of birth control by FCBP. Among FCBP who respond-

Table IV. Distribution of voluntary survey respondents by risk category

Risk category	Phase 1			Phase 2		
	agreed to participate	no. surveyed	respondents [n (%)]	agreed to participate	no. surveyed	respondents [n (%)]
Females of childbearing potential	186	183	134 (73.2)	102	77	44 (57.1)
Adult males (≥18 years)	5013	1602	1175 (73.3)	2621	1289	962 (74.6)
Adult females not of childbearing potential	3418	1058	819 (77.4)	1815	852	651 (76.4)
Males (aged 12–17 years)	1	1	1 (100.0)	1	1	0
Children <18 years	5	5	2 (40.0)	0	0	0
Total	8623	2849	2131 (74.8)	4539	2219	1657 (74.7)

ed to the survey questions, >81% answered correctly to the behavioural questions.

Table VIII presents birth control compliance by risk category. Compliance was higher during phase 1 than in phase 2.

2.4 Pharmacy Audits

An average of ten random prescriptions and counselling records at each pharmacy were evaluated for compliance with the RevAssist® programme. The auditors found an overall 97% compliance rate for the reviewed records. The majority of the observations documented during the audits were related to (i) prescription and counselling accuracy such as undocumented patient risk type, lack of patient counselling and undocumented counselling; and (ii) pharmacy dispensing controls such as dispensing outside the approved timeframe, dispensing without obtaining a confirmation number from Celgene, dispensing more than a 28-day supply and dispensing without a valid confirmation number.

Table V. Distribution of responses to receipt of patient information brochure and pharmacist counselling on lenalidomide by risk category during phase 1 of the voluntary survey

Responses	Risk category [n (%)]	
	FCBP (n = 134)	adult males[a] (n = 1175)
Received brochure on Revlimid®	118 (88.1)	1077 (91.7)
Read brochure on Revlimid®	117 (87.3)	1060 (90.2)
Pharmacist discussed Revlimid® treatment	121 (90.3)	934 (79.5)
Pharmacist provided patient information	122 (91.0)	934 (83.7)
Understood pharmacist	123 (91.8)	1000 (85.1)

a Aged ≥18 years.

FCBP = female patients of childbearing potential.

2.5 Pregnancy Test Results

During the covered period, there were four reports of false-positive β-human chorionic gonadotrophin (hCG) measurements and no reports of pregnancy for FCBP and female partners of male patients in the Celgene global safety database. The age of the patients with elevated β-hCG was 43–57 years and the indication for lenalidomide use was multiple myeloma. The β-hCG levels ranged from 6–12 IU/L. The duration of treatment at the time of the first elevated β-hCG ranged from 2 to 8 weeks. One patient (43 years of age) had a medical history of elevated β-hCG. Upon medical review, lenalidomide release was authorized in three patients and discontinued in one patient due to a serious adverse event unrelated to the pregnancy test.

3. Discussion

RevAssist® is a risk minimization programme that was designed to prevent fetal exposure to lenalidomide.

The programme uses the various tools of a risk minimization programme that were identified by Uhl et al.,[6] including product labelling (e.g. black-box warning, wording of the contraindication and warning section, medication guide, recommenda-

Table VI. Key knowledge questions identified as 'true' among female patients of childbearing potential (FCBP) and adult males (age ≥18 years) during phases 1 and 2 (voluntary survey)

Knowledge questions	Phase 1 [n (%)]		Phase 2 [n (%)]	
	FCBP (n = 134)	males (n = 1175)	FCBP (n = 44)	males (n = 962)
Women should not get pregnant while taking Revlimid®	132 (98.5)	NA	43 (97.7)	NA
Revlimid® may cause birth defects	132 (98.5)	1147 (97.6)	43 (97.7)	928 (96.5)
Women who could get pregnant need to use two different types of birth control	130 (97.0)	NA	43 (97.7)	NA
Birth control pills cannot be used alone to prevent pregnancy while taking Revlimid®	131 (97.8)	NA	42 (95.5)	NA
It is important to stop taking Revlimid® before trying to get pregnant	131 (97.8)	1142 (97.2)	41 (93.2)	917 (95.3)
Men should use condoms while on Revlimid® if they are sexually active with a woman who is able to get pregnant	NA	1154 (98.2)		924 (96.0)

NA = not applicable (question was not part of survey).

tions for pregnancy testing and contraception), education (e.g. brochures, patient medication guides and training programmes), reminder systems (e.g. verification of authorized provider and computerized prescriber surveys) and restricted distribution (e.g. limited supply, dispensing by contract pharmacies, registration of prescribers and pharmacies). The programme also includes the evaluation plan, physician-patient agreements, surveys and the ability to track product movement through the programme.

Table VII. Birth control use by risk category[a] (voluntary survey)

Birth control methods	FCBP [n (%)]		Males aged ≥18 y [n (%)]	
	phase 1	phase 2	phase 1	phase 2
No. of respondents	134	44	1175	962
Abstinence	64 (47.8)	9 (20.5)	740 (63.0)	156 (16.2)
Birth control pills, patch, cervical ring or birth control injections	41 (30.6)	9 (20.5)	71 (6.0)	17 (1.8)
Intrauterine device or diaphragm	26 (19.4)	5 (11.4)	41 (3.5)	3 (0.3)
Cervical cap or sponge	15 (11.2)	3 (6.8)	36 (3.1)	6 (0.6)
Natural birth control methods	NA	NA	52 (4.4)	10 (1.0)
Rhythm method	10 (7.5)	3 (6.8)	NA	NA
Condom	78 (58.2)	17 (38.6)	319 (27.1)	97 (10.1)
Tubal ligation (sterile)	26 (19.4)	5 (11.4)	NA	NA
Change of life (menopause)	42 (31.3)	10 (22.7)	NA	NA
Unable to get pregnant	27 (20.1)	5 (11.4)	NA	NA
Vasectomy	22 (16.4)	5 (11.4)	231 (19.7)	100 (10.4)
Spermicidal cream or foam	NA	NA	41 (3.5)	9 (0.9)
Female partner cannot get pregnant because of menopause or hysterectomy	NA	NA	514 (43.7)	193 (20.1)
Female partner cannot get pregnant because of chemotherapy or other medical therapies	NA	NA	83 (7.1)	19 (2.0)
Other method of birth control	12 (9.0)	1 (2.3)	67 (5.7)	18 (1.9)
None	0	NA	197 (16.8)	54 (5.6)

a The RevAssist® requirement is the use of two forms of birth control. A survey respondent may have chosen more than one method of birth control.

FCBP = female patients of childbearing potential; **NA** = not applicable.

Table VIII. Birth control compliance by risk category (voluntary survey)

Compliance	FCBP [n (%)]		Males aged ≥18 y [n (%)]	
	phase 1	phase 2	phase 1	phase 2
No. of respondents	134	44	1175	962
Compliant	109 (81.3)	23 (52.3)	1011 (86.0)	344 (35.8)
Not compliant	25 (18.7)	21 (47.7)	164 (14.0)	618 (64.2)

FCBP = female patients of childbearing potential.

Although RevAssist® is implemented in the context of a very low risk of pregnancies given the low proportion of FCBP (2.1%), the percentage of male patients taking lenalidomide who may impregnate women is high (56%) and the consequence of fetal exposure, should it occur, is of concern.

While there have been no reports of pregnancy in FCBP or female partners of male patients in the RevAssist® programme, there were four reports of false-positive β-hCG measurements in patients aged 43–57 years. There are numerous causes of false-positive hCG tests, including detection of pituitary hCG, free hCG β-subunit production, interference by non-hCG substances, and others. It has been reported that pituitary hCG circulates in low concentrations in premenopausal women, but the concentrations rise in perimenopausal and postmenopausal women.[11] Similarly, serum hCG concentrations have been reported to be higher for nonpregnant women aged >55 years (<2.0–13.1 IU/L) than in nonpregnant women aged 18–40 years (<2.0–4.6 IU/L) and 41–55 years (<2.0–7.7 IU/L).[12]

The mandatory survey questions showed more responses among prescribers on the questions related to natural menopause and surgical removal of the uterus. The discrepancies were attributed to the prescriber needing to complete the mandatory survey for every prescription while the FCBP completes the mandatory survey once a month. In the event of dosage adjustment where a prescription is written, the prescriber is required to complete the mandatory survey. The mandatory survey question with the most number of responses that diverged from the desired answers was the date of the pregnancy test. RevAssist® requires pregnancy tests within 10–14 days and again within 24 hours before lenalidomide is prescribed, weekly during the first 4 weeks, then every 4 weeks during treatment if menses are regular and every 2 weeks if the menses are irregular.

The response rate to the voluntary patient surveys was relatively high (73%) for both FCBP and adult males during phase 1. The response rate was still high (74%) for the males but decreased to 57% for FCBP during phase 2. The reasons for the low response rate of FCBP to the phase 2 survey questions were not immediately clear, and this is being monitored and investigated. The voluntary patient surveys during the first year of lenalidomide availability in the market showed that the majority of FCBP and adult males in both phases had an understanding of key questions regarding knowledge of the risks of lenalidomide use and behaviours necessary to minimize risks. However, compliance with methods of contraception and appropriate risk reduction behaviours were different between the two phases. While overall compliance in phase 1 was >80%, compliance in the phase 2 was <52%. The low compliance in the voluntary surveys was attributed partly to a significant number of FCBPs and adult males who did not answer some key questions necessary to calculate compliance and were therefore classified as noncompliant. Revision of the current algorithm to avoid this is currently being explored.

The risk management intervention specialists are heavily involved in the resolution of either type of discrepant response in both the mandatory and voluntary surveys. A risk management intervention specialist immediately contacts the prescribers to resolve any discrepancy. More than 99% of the time, the intervention resulted in resolution of the discrepant responses in the survey.

The pharmacy audit findings during the first year of lenalidomide in the market showed the com-

pliance with RevAssist® is high. Deficiencies were communicated to pharmacy management, and corrective actions were discussed to ensure complete understanding of the programme requirements and ensure compliance. Celgene has instituted corrective actions to improve compliance such as retraining of pharmacists involved in the programme, increasing contact with pharmacies and implementing additional tools to assist the pharmacies in better understanding the requirements.

4. Conclusion

The RevAssist® programme is labour-intensive, time-consuming and costly, but continues to be effective in preventing fetal exposure. Undertaking such a programme, even in a patient population with a low percentage of FCBP, is very well justified considering the fetal outcome should a pregnancy occur.

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